

The American Journal of DIGESTIVE DISEASES

An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

PHYSIOLOGICAL STUDY OF THE TWO PROTEASES OF THE GASTRIC JUICE— <i>Michel J. Demole and Gerard Milhaud, M. D.</i>	43
ARE ACHLORHYDRIA, ACHYLIA GASTRICA AND PERNICIOUS ANEMIA PRECANCEROUS CONDITIONS?— <i>Fredrick S. Weinberg, M. D.</i>	45
COMPLICATIONS OF CHRONIC ULCERATIVE COLITIS— <i>Merton L. Brown, M. D., Anthony M. Kasich, M. D. and Berthold Weingarten, M. D.</i>	52
AN APPRAISAL OF THE PSYCHOLOGICAL RELATIONSHIP OF CORONARY DISEASE TO PEPTIC ULCER— <i>Maurice Feldman, M. D. and Samuel Morrison, M. D.</i>	55
IMMEDIATE AMBULATION— <i>Alfred J. Cantor, M. D.</i>	56
SUCCESSFUL OINTMENT THERAPY FOR PRURITUS ANI— <i>Laurence G. Bodkin, M. D. and Edgar A. Ferguson, Jr.</i>	59
CHRONIC PEPTIC DUODENAL ULCER WITH CANCEROUS TRANSFORMATION— <i>E. F. Geever, M. D., V. L. Bolton, M. D. and N. W. Fawcett, M. D.</i>	61
A CASE OF ACUTE CHOLANGITIS (POST-OPERATIVE) DUE TO <i>PROTEUS VULGARIS</i> SEPSIS TREATED WITH AUROMYCIN— <i>A. Allen Goldbloom and Maurice Golbey, M. D.</i>	63
INCOMPLETE OBSTRUCTION OF THE SMALL INTESTINE— <i>Alexander Strelinger, M. D.</i>	66
DEMONSTRATION OF A TUMOR INVOLVING THE PANCREAS THROUGH THE USE OF DUODENAL DRAINAGE AND THE INTRAVENOUS INJECTION OF SECRETIN— <i>N. R. Bothreau, M. D., F. H. Draper, M. D. and G. E. Gibbs, M. D.</i>	70

ABSTRACTS ON NUTRITION, EDITORIAL, BOOK REVIEWS, GENERAL ABSTRACTS OF CURRENT LITERATURE	71-75
--	-------

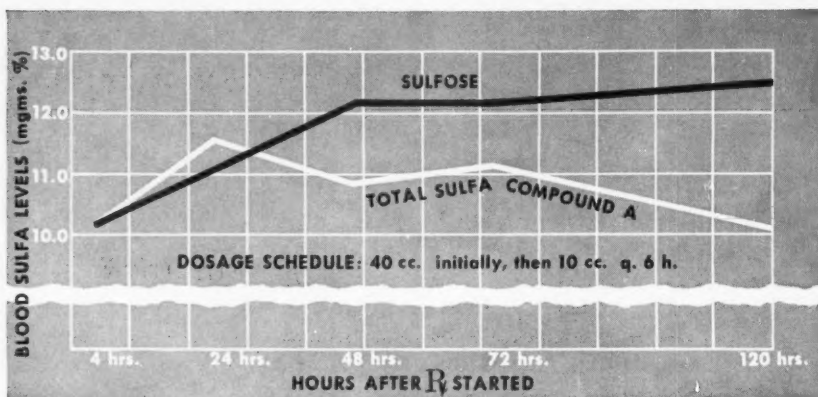
Volume 18

February, 1951

Number 2

Copyright 1951, Sandfield Publishing Company

A New and Better Triple Sulfonamide Suspension that provides higher, sustained blood levels



A comparison of blood sulfonamide levels on equal doses of SULFOSE and a control preparation having the same sulfonamide composition.

SULFOSE contains sulfadiazine, sulfamerazine and sulfamethazine suspended in a unique, flavored vehicle containing a special alumina gel.

- Unusually palatable
- Stabilized suspension—won't separate
- Easy to measure—pours freely

Each teaspoonful (5 cc.) contains 0.5 Gm. total sulfonamides—0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

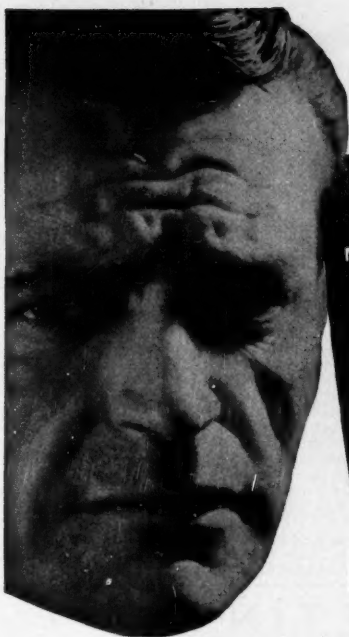
SUPPLIED in bottles of 1 pint.

SULFOSE[®]

TRIPLE SULFONAMIDE SUSPENSION



WYETH Incorporated, Philadelphia, Pa.



The seemingly
intractable
ulcer patient

His pain is severe
His recurrences are frequent
He bleeds repeatedly
He is easily constipated

This "hard-to-keep-well" ulcer patient need not be a cause for undue concern until Tricreamalate has been given adequate trial. When other medications fail, Tricreamalate, a combination of specially prepared gastric antacids with distinct advantages will often

stop pain more quickly
prevent recurrences
control bleeding
without side effects

Tricreamalate is a highly reactive amorphous acid soluble aluminum hydroxide plus hydrated magnesium trisilicate. Tablets: 2 to 4, after each feeding. Liquid: 2 to 4 teaspoonfuls after each feeding.

TRICREAMALATE, TRADEMARK REG. U. S. & CANADA

Tricreamalate
Brand of Aluminum Hydroxide Gel and Magnesium Trisilicate

Winthrop-Stearns INC. NEW YORK 18, N. Y. • WINDSOR, ONT.

THE OLDEST PERIODICAL IN ITS SPECIAL FIELD ON THE WESTERN HEMISPHERE

Printing Office:
117 E. MAIN ST.
BERNE, INDIANA

Business and Editorial Office:
425 LINCOLN BANK TOWER
FORT WAYNE 2, INDIANA

Advertising Office:
Vining & Meyers
35 EAST WACKER DRIVE
CHICAGO 1, ILLINOIS

ANNUAL SUBSCRIPTION RATE \$6.00; TWO YEARS, \$10.00

SINGLE COPIES: CURRENT YEAR 80c. BACK YEARS \$1.00.

Editor: BEAUMONT S. CORNELL
FORT WAYNE, INDIANA

Foreign Subscriptions \$7.00; two years \$12.00

Regional Editor: FRANZ J. LUST
17 E. 89TH ST., NEW YORK, N. Y.

EDITORIAL COUNCIL

CLINICAL MEDICINE—DISEASES OF DIGESTION: Anthony Bassler; John M. Blackford; Leon Bloch; Arthur Leonard Bloomfield; Russel S. Boles; Joseph Edmond Dube; Edward S. Emery, Jr.; George B. Eusterman; Harry Gauss; Frank D. Gorham; Russell L. Haden; R. H. M. Hardisty; Charles Lester Hartsock; Blair Holecomb; Harry G. Jacobi; Allen A. Jones; Chester M. Jones; Clement Russell Jones; Noble Wiley Jones; Joseph William Larimore; Jean Roger Arthur LeSage; B. B. Vincent Lyon; Lay Martin; Francis D. Murphy; Moses Paulson; George M. Piersol; Milton M. Portis; Martin Rehfuess; Vernon C. Rowland; Adolph Sachs; Leon Schiff; Daniel M. Silverman; Virgil E. Simpson; Albert M. Snell; Horace W. Soper; Cyrus Cressey Sturgis; Martin G. Vorhaus. **GASTROSCOPY, ESOPHAGOSCOPY:** James L. Borland; E. B. Freeman; Chevalier Jackson; Rudolf Schindler; Porter Paisley Vinson. **NUTRITION:** Lloyd Arnold; Clifford Joseph Barborka; Reginald Fitz; Seale Harris; Henry L. John; Howard Frank Root; Nina Simmonds. **SURGERY OF THE LOWER COLON AND RECTUM:** Louis Arthur Baile; Jerome Morley Lynch; Clement L. Martin; Curtis Rosser; Louis J. Hirschman; Frank C. Yeomans. **BACTERIOLOGY:** Oscar Felsenfeld. **THERAPEUTICS:** Walter A. Bastedo. **ALLERGY:** Albert H. Rowe; J. Warriek Thomas; **ROENTGENOLOGY:** David S. Beilin; Arthur C. Christie; Frederick J. Hodges;

William H. Stewart. **PARASITOLOGY:** Robert Hegner; Kenneth Merrill Lynch; Thomas Byrd Magath; Henry Meloney. **EXPERIMENTAL PHYSIOLOGY:** J. P. Quigley; A. J. Carlson; M. H. F. Friedman; Ira A. Manville; Edward J. Van Lier. **PSYCHIATRY AND NEUROLOGY:** William C. Menninger. **ABDOMINAL SURGERY:** Albert A. Berg; Thomas M. Joyce; Rudolph Matas; Edward Wm. Alton Ochauer; James Taft Pilcher; Charles T. Sturgeon.

Published Monthly at 117 East Main St., Berne, Ind.

Correspondence regarding advertising must be addressed to Vining and Myers, 35 E. Wacker Drive, Chicago. Advertising plates must be sent to C. H. Sprunger, 117 E. Main St., Berne Indiana. Subscriptions, reprint orders, etc., may be addressed to 117 E. Main St., Berne Ind., or to 425 Lincoln Bank Tower, Fort Wayne 2, Ind. Manuscripts and books for review must be addressed to Beaumont S. Cornell, 425 Lincoln Bank Tower, Fort Wayne 2, Ind. Illustrations in excess of six per article are charged at cost to the author. Contents of Journal are fully copyrighted. Copyright 1950, by Sandfield Publishing Co., 425 Lincoln Bank Tower, Fort Wayne, Ind., in the U.S.A., Vol. 18, No. 2, February, 1951. Entered as second class matter, Sept. 6, 1950, at the Post Office at Berne, Indiana, under the Act of March 3, 1879.

RAMETIN READILY AVAILABLE FOR USE IN YOUR DAILY PRACTICE

RAMETIN (Crystalline Vitamin B-12 U.S.P.) is readily available, through your regular source of medical supplies. Your pharmacist is prepared to fill your prescriptions for use of this—*antipernicious factors of liver—a pure, crystalline compound of extremely high potency, in your daily practice.*

RAMETIN has been widely accepted by the medical profession and contains the **ONLY** Vitamin B12 accepted by the U.S.P., XIV.

TO MAKE VITAMIN B-12 THERAPY MORE ECONOMICAL

Specify **RAMETIN**

RAMETIN TABLETS—the first oral Vitamin B-12. Palatable, candy-like in taste, soluble, scored tablets containing Crystalline Vitamin B-12, U.S.P., XIV.

RAMETIN TABLETS available in three potencies:
5 microgram tablets, bottle of 25 and 100.
10 microgram tablets, bottle of 100.
30 microgram tablets, bottle of 100.

FOR PARENTERAL ADMINISTRATION—RAMETIN INJECTION

A.M.A. COUNCIL ACCEPTED

10 CC. multiple dose vials in two potencies

10 micrograms and 15 micrograms

Crystalline Vitamin B-12 U.S.P., XIV. per CC.

LITERATURE AND SAMPLES GLADLY SUPPLIED

BIO-RAMO DRUG CO., INC.

Baltimore 1, Md.

MEAT...and the PROTEIN NEEDS of the DIABETIC

Not less but *more protein* than the traditional gram per kilo of body weight recommended for the non-diabetic individual promotes an increased sense of well-being in the diabetic patient. Liberal amounts of biologically excellent protein, such as that provided by *meat*, are therefore especially useful in dietotherapy.

For supporting the well-being and vigor of the patient, increasing his resistance to infection, and minimizing many of the degenerative changes common in diabetes mellitus, maintenance of body protein reserves is particularly important.^{1,2} The former belief that protein foods, especially meat, engender hypertension and arteriosclerosis, is no longer tenable. On the contrary, deficits in dietary protein are apt to initiate anemia, hypoproteinemia, and retrogressive processes in the kidneys and other organs or tissues.

Ample amounts of high-quality protein foods in the prescribed diet—including generous amounts of meat—are important for maintaining a good nutritional state in the diabetic patient. Such a diet provides the nutritional essentials required in overcoming infections and in prompter healing of traumatic wounds.

Meat, however, is valuable to the patient for more than just its biologically excellent protein. It also furnishes important amounts of iron, thiamine, riboflavin and niacin, and of the newly discovered vitamin B₁₂ which, among its several functions, promotes efficient utilization of protein.

(1) Mosenthal, H. O.: Management of Diabetes Mellitus: An Analysis of Present-Day Methods of Treatment, Ann. Int. Med., 29:79 (July) 1948.

(2) McLester, J. S.: Nutrition and Diet in Health and Disease, 5th ed., Phil., W. B. Saunders Company, 1949, page 364.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.



American Meat Institute
Main Office, Chicago...Members Throughout the United States

NEW

Resin-gastric ● mucin combination

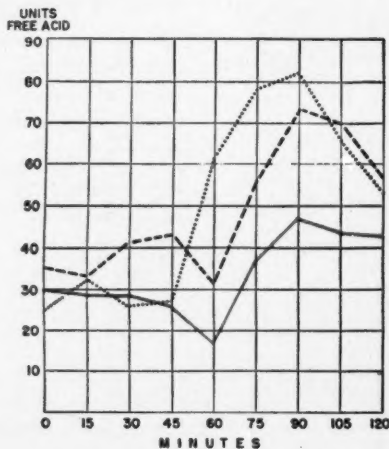
*in peptic ulcer management**

combines

"...the good effects of resins with those of gastric mucin in the treatment of gastroduodenal ulcer"*

"...the admixture of gastric mucin enhances the antacid effect of the resins..."*

..... Histamine
..... Resamine and
Antac Exchange Resin and Mucin
Combination, 4 Tablets.
..... Histamine and
Antac Exchange Resin and Mucin
Combination, 2 Tablets.



STEIGMANN AND SCHLESINGER* in the Gastrointestinal Clinic of the Cook County Hospital, Chicago, made a five year study of the effects of available antacids in the treatment of gastroduodenal ulceration.

Various resinous substances were tested including "the new type of 'antacid'"—Resmicon—a synergistic combination of a finely dispersed ion-exchange polyamine resin with a specially processed form of gastric mucin.

Resmicon was given to a series of patients over a period of 2 to 15 months. Most of the patients chosen were those who did not respond well to therapy with other antacids.

EFFECT ENHANCED—The investigators confirmed their previous findings** namely that "the admixture of gastric mucin enhances the effect of the resins."

QUICK RELIEF—"Most patients

had good symptomatic relief within the first week (two to seven days) of 'Resmicon' treatment . . .

"They felt better, ate better and gained weight. The majority took the tablets well and there were no complaints regarding constipation or diarrhea."

HEALING ENCOURAGED—"Simultaneously with clinical improvement the patients with gastric ulcer showed significant changes in the size of the craters when x-rays were taken at weekly or bi-monthly intervals.

"Those who were gastroscoped (a total of 19) also showed healing of the ulcer."

"This new substance [Resmicon] appears to combine the good effects of resins (neutralization of the hydrochloric acid in gastric juice without interfering with the acid-base balance) with those of gastric mucin in the treatment of gastroduodenal ulcer."

Resmicon®

ACID ADSORBENT DEMULCENT • 84 TABLETS

*Steigmann, F., and Schlesinger, R. B.: A Resin-Gastric Mucin Mixture in the Medical Management of Peptic Ulcer, *American J. Dig. Dis.* 17:361-365 (Nov.) 1950.

**Scientific Exhibit of the A. M. A., Atlantic City Session, 1949.

Whittier
LABORATORIES

DIVISION NUTRITION RESEARCH LABORATORIES, INC.
CHICAGO 11, ILLINOIS

MISTER BULLENBEAR

is a vitamin square



Whether he's a worried tycoon too busy to eat or an anorectic toper or smoker, if the patient is subclinically vitamin deficient, he'll benefit from dietary reform and DAYAMIN capsules. These little vanilla flavored capsules are easy to swallow. One daily as a supplement; two or more for therapeutic use—see formula. In bottles of 30, 100 and 250. Patients who don't like capsules enjoy DAYAMIN Liquid—with the citrus-like flavor and odor. In bottles of 90 cc., 8 fluidounces and 1 pint. *Abbott*

Each DAYAMIN capsule contains:
 Vitamin A 10,000 U.S.P. units
 Vitamin D 1,000 U.S.P. units
 Thiamine Hydrochloride 5 mg.
 Riboflavin 5 mg.
 Nicotinamide 25 mg.
 Pyridoxine Hydrochloride 1.5 mg.
 Pantothenic Acid (as
 calcium pantothenate) 5 mg.
 Ascorbic Acid 100 mg.

Prescribe

DAYAMIN®

(ABBOTT'S MULTIPLE VITAMINS)



A POTENT ANTICHOLINERGIC

*Controls visceral
spasm by
central and
local action*

Formulas

Each teaspoonful (5 cc.) of
ELIXIR HYBEPHEN
contains:

Phenobarbital..... $\frac{1}{4}$ gr.
Tr. Belladonna.....5 min.
Tr. Hyoscyamus...15 min.
in a pleasant tasting vehicle.

Each **HYBEPHEN TAB-
LET** provides:

Phenobarbital..... $\frac{1}{4}$ gr.
Tr. Belladonna.....5 min.
(equiv.)
Tr. Hyoscyamus...15 min.
(equiv.)

Dosage:

1 tablet every 4 hours.

The anticholinergic action of Elixir Hybephen is specifically indicated in pylorospasm, cardiospasm, spasticity of the colon and emotional diarrhea, when due to parasympathetic hyperactivity.

This dual acting antispasmodic is widely preferred because:

- All the *natural* alkaloids of belladonna and hyoscyamus are provided, making for a smoother action than atropine alone.
- The small total amount of atropine in this mixture reduces the incidence of undesirable side effects.
- Rigid assay of tincture of belladonna and tincture of hyoscyamus assures uniformity in anticholinergic potency.
- The presence of phenobarbital aids in controlling increased psychomotor tension, frequently a factor in parasympathetic spasm.

The dose of Elixir Hybephen is 1 teaspoonful every four hours. This schedule produces a maintained and continuous antispasmodic action.

THE S. E. MASSENGILL COMPANY

Bristol, Tenn.-Va.

NEW YORK • SAN FRANCISCO • KANSAS CITY



HYBEPHEN

Elixir and Tablets

in intractable peptic ulcer

KUTROL[®]

UROENTERONE, PARKE-DAVIS

PEPTIC ULCER INHIBITANT

when other therapy fails

Beneficial response in up to 70 to 80 per cent of cases —

Noteworthy results in chronic cases of Duodenal and Jejunal Ulcers having frequent recurrences and resistant to intensive conventional therapy.

Remission of ulcer often within 3 to 6 weeks —

Rapid relief of symptoms and disappearance of ulcer crater.

Simplified regimen —

Normal three-meals-a-day schedule soon after treatment begins.

Well-tolerated —

Does not inhibit gastric secretion. No toxicity or idiosyncrasy noted.

DOSAGE: Two KUTROL Kapsels[®] four times daily, one-half hour before mealtime and at bedtime.

PACKAGING: KUTROL Kapsels[®], 75 mg., are supplied in bottles of 100.

Descriptive Literature Available On Request.

PARKE, DAVIS & COMPANY



PHYSIOLOGICAL STUDY OF THE TWO PROTEASES OF THE GASTRIC JUICE

MICHEL J. DEMOLE, M.D., and GÉRARD MILHAUD, M.D., Sc.D., Geneva, Switzerland.*

IN 1940 Freudenberg (3) and Buchs studied the digestion of the milk proteins by nursing infants. They wondered how this digestion could take place with a gastric chyme, the pH of which (4, 5) did not enable pepsin to react. They refused to admit, as Michaelis did, "that a gastric juice of pH 3 digests protides very poorly; that at pH 4 it digests them hardly at all; and that this fact is even more evident in the case of nursing infants in whose stomachs the hydrogen ion concentration is lower (pH 5)." They determined the curve of activity of the gastric juice of a normal nursing infant between the pH of 1 to 6, using skim milk as substratum; and they were surprised to find that this curve was totally different from that which Sørensen had obtained for pepsin. The optimum of digestion is placed at pH 3.3; at pH 4.7 the proteolytic activity remains very important. They are therefore obliged to postulate the presence in the gastric juice of a *second proteolytic ferment*, acting in a medium much less acid than that of pepsin, and secreted in equal or higher quantities. They were able to separate the activity of each of these two ferments, inhibiting peptic activity by conducting the digestion at 70° C, and that of the new ferment by adding uranyl acetate or aluminum salt. The new protease, activated by cyanide and by the thiol groups, could be put in the same category as the *cathepsins* of Willstätter and Bamann (9). These two authors had put in evidence, in 1929, the existence in the gastric mucosa of an endoferment which splits in a slightly acid medium. They were so assured of the leukocytary origin of this ferment that they did not even search for it in the gastric juice. It is astonishing that after the discovery of pepsin, one of the oldest known and most studied ferments, it has taken a 100 years to reveal the existence of the second protease of gastric juice. An amazing number of mishaps underlies this fact.

UNITY OR DUALITY OF THE TWO GASTRIC PROTEASES?

Crystallized pepsin contains the two proteases* in the same proportion as normal gastric juice. This can be explained as follows:

I. By *two ferments*, the physico-chemical properties of which are sufficiently similar so that they crystallize together.

II. By *two groups fixed on the same molecule* and possessing, according to the acidity of the solution, different enzymatic activities.

We have endeavored to solve this problem through

*From the Medical Policlinic (Prof. E. Martin), University of Geneva, Switzerland.

Submitted May 4, 1950.

*Measurement of proteolytic activity. We have adopted the technique of Buchs and Freudenberg (1) employing Edestine as substratum. The precision of this technique is within about 5%, which is quite satisfactory. After the digestion, the undigested edestine is precipitated by sulfosalicylic acid, and the intensity of the turbidity is determined by the photocolormeter.

separation tests (5) which were carried out at the Pasteur Institute, Paris. The adsorption and elution of a solution of crystallized pepsin have not enabled us to isolate one enzymatic activity from the other. Ultracentrifugation did not permit it either. Electrophoretic analysis at pH 4 showed that crystallized pepsin contained a principal component (83.5%), beside three other constituents present in weak concentrations. Finally, flotation, a procedure which permits, in a solution, the separation of substances with low, of those with high superficial tension, did not succeed further in yielding a separation of the two ferments.

In these circumstances, we had to admit the existence of one only ferment with a double activity.

ACTIVE GROUPS OF THE PEPSIN MOLECULE

The importance of the integrity of the tyrosine groups for the activity of pepsin is well known. We found that the iodation or the diazotisation of the tyrosine radicals caused as well the disappearance of the activity of the second proteolytic ferment of the gastric juice.

We have never obtained an activation of the second protease by potassium cyanide nor by the thiol groups, using edestine as the substratum. For this reason we renounced the use of the name "gastric cathepsin," as we did first (2), to designate the second proteolytic ferment. We propose to call it "pepsin or protease II" conserving the name "pepsin I" for the ferment discovery by Schwann in 1936.

PHYSIOLOGICAL STUDY

1. Gastric juices.

Normal human gastric juice contains, beside pepsin, another protease in equal or even slightly higher quantities, the digestive curve of which is exactly similar to that of crystallized pepsin (Figure 1).

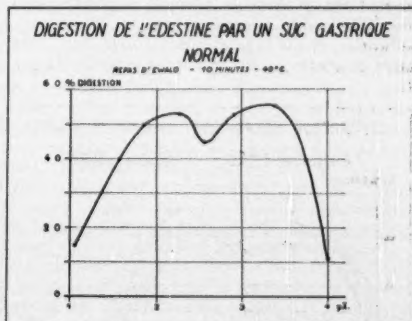


Figure 1

CONSTANCY OF THE SECRETION OF THE FERMENTS

During the course of a fractionized gastric test, the secretion of free or total hydrochloric acid is subject

to great variations from one sampling to another, and 6 different specimens have usually to be taken at intervals of $\frac{1}{4}$ hour to find out the rate of maximum acidity. It is surprising to find that *during this test, the tenure in ferments is quite constant* (Figure 2), on condition that the pH is not too high, which would render the proteases inactive. Therefore the dosage of the proteases in a single specimen furnishes information of more constant value than that furnished by the determination of the hydrochloric acid, secreted in varied quantities during the course of a gastric juice test.

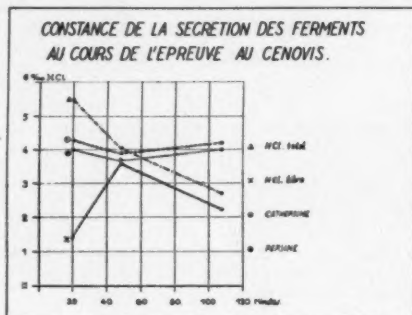


Figure 2

INCITANTS AND THE SECRETION OF FERMENTS

Varied incitants: Ewald's meal (toasts and light tea), Cenovis (an extract of yeast), histamine, insuline provoke in the same individual approximately the same fermentary reaction (5). We have not found an incitant, specific for the secretion of one protease to the exclusion of the other, which is easily explained if one admits the secretion of a single ferment with a double activity. We reproduce below the charts of gastric tests after excitation with histamine or with insuline of a normal individual (Fig. 3). It can be seen that the quantity of ferment is greater with insuline than with histamine without, however, any modification in the type of curve. One notes also the relative constancy of the tenure in protease during the tests.

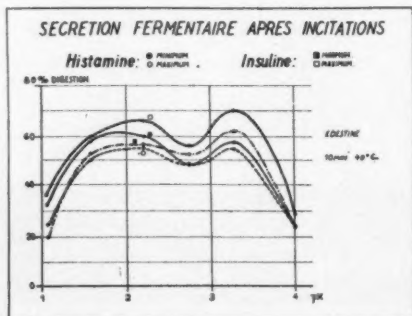


Figure 3

AVERAGE AMOUNT OF PROTEASE IN NORMAL GASTRIC JUICE

Before studying the proteolytic activity of pathological gastric juice, the normal rate of digestion had to be fixed. Buchs (1) found in seven normal subjects an average enzymatic activity of 43% for pepsin and 54% for the second ferment. For ourselves, we obtained the following results:

Sex Age	Incitant	HCl free	total	Pepsin	Protease II
M. 35	Ewald	0.8	1.3	48	50
M. 28	Cenovis	0.9	1.6	50	55
F. 32	Cenovis	1.0	1.9	45	48
M. 25	Histamine	1.5	3.0	45	47
F. 40	Cenovis	1.4	2.6	52	60
				48%	52%

AVERAGE RATES

We consider as pathological a digestion superior to 70% or inferior to 40%, which leaves a large margin for physiological variations. Moreover, a proteolytic activity of the second ferment distinctly inferior to that of pepsin, leads one to suspect a pathological condition even when the rates of digestion are sufficient.

2. Gastric proteases in the blood:

In 1908, Loeper showed that the digestive tract is capable of resorbing pepsin, which can be found later in the urine. It must pass, therefore, through the blood, and in 1922 he observed (4) that serum contained in fact a proteolytic ferment acting in a strongly acid medium. He brought about the digestion of the blood proteins and put in evidence the peptones by the biuret reaction. The physiological variations of pepsinemia are a function of the gastric secretion, they rise and fall with it.

We asked ourselves what happened to the second protease in the blood?

We brought the pH of fresh serum to 5.5 by the addition of 1/N hydrochloric acid. Then we introduced 0.15 cc. of serum into 5 cc. of a solution of hydrochloric or acetic acid of the same concentration as for the preparation of solutions of edestine. The preparation is left in the incubator at 40°C., then the undigested proteins are precipitated exactly as described for edestine. The reading is made with a formerly calibrated photometer. The following curve of digestion was obtained (Fig. 4).

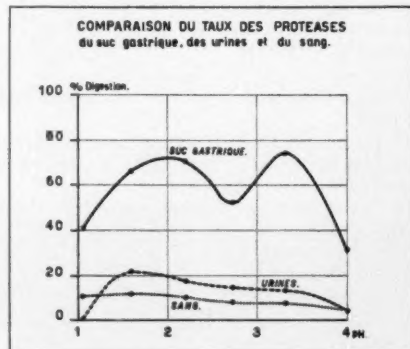


Figure 4

One sees that the digestion of pepsin is slightly superior to that of the second protease, which is explained by the fact that the pH of serum, superior to 7, inactivates the major part of these enzymes.

3. Gastric proteases in the urine:

In 1874, Brücke showed that normal urine contained pepsin. Sahli (1885) found that morning urine possessed the strongest enzymatic power, and that of the afternoon, the weakest. Peczenik reconsidered (7) this question in 1928 and noted that the proteolytic activity of urine increased with digestion and diminished during the fasting period. It depended on the condition of the gastric mucosa and of the kidney. Von Noorden (6) observed that the urinary excretion of pepsin increased in the case of kidney trouble and during periods of fever. Rothschild could not discern (8) any pepsin in the urine in the case of Addison's anemia, even after an injection of histamine, while gastric cancer did not exclude the presence of urinary pepsin.

We searched for pepsin and the second protease in urine, by adding 0.2 cc. of urine to 2.5 cc. of a solution of edestine. After 40 min. of digestion at 40° C., we precipitated the unattacked edestine in the usual manner. It is very important that the pH of the urine be not superior to 6-6.5, otherwise one risks to find only trace of the proteolytic ferments. But even in a more acid urine (e.g. pH 5) one finds mostly pepsin, of which the pH of optimum activity is displaced on the acid side (towards pH 1.5) as is shown in Figure 4.

In conclusion, we see that the proteolytic enzymes of the stomach pass into the blood and urine, and that

pepsin retains an activity superior to that of the second protease in the course of this process.

SUMMARY

The work of Freudenberg and Buchs permitted a more penetrating study of protein digestion of the nursing infant and even of the adult. It appears quite likely that protease II assumes the more important role in gastric digestion, since it requires a relatively high pH (3.3) while pepsin I only digests in a strongly acid solution.

It was interesting, besides, to study the secretion of ferments in the course of a fractionizing gastric test, and to note that the tenure in ferment remained sensibly constant during this test.

Finally, we searched for the gastric proteases in the blood and in the urine.

REFERENCES

1. Buchs, S.: *Die Biologie des Magenkathepsins*; S. Karger, Baale, New-York, 1947.
2. Demole, M. and Milhaud, G. *Arch. Malad. appar. digest.*; 38, 1186, 1949.
3. Freudenberg, E.: *Enzymologia*; 8, 385, 1940.
4. Loeper, M. and Debray, C.: *C. R. Soc. Biol.*; 86, 344, 1922.
5. Milhaud, G., Demole, M. J. and Epiney, J.: *Helv. med. Acta*; 16, 244, 1949.
6. von Noorden, C.: *Pathologie des Stoffwechsels*; Berlin 221, 1923.
7. Peczenik, O. and Kavahra, M.: *Fermentforsch.*; 9, 97, 166, 1928.
8. Rothschild, I. A.: *Arch. Verdauungskrankh.*; 47, 232, 1930.
9. Willstätter, R. and Bamann, E.: *Z. physiol. Chem.*; 180, 127, 1929.

ARE ACHLORHYDRIA, ACHYLIA GASTRICA AND PERNICIOUS ANEMIA PRECANCEROUS CONDITIONS?

FREDERICK S. WEINBERG, M. D., New York, N. Y.

ONE OF THE MAJOR problems in medicine today is that of making a sufficiently early diagnosis of cancer of the stomach. As we know, by the time the patient shows any symptoms, the disease is usually too far advanced for surgical results to be very successful. It is in an effort to remedy this situation that systematic x-ray examinations of the population have been made as an effort to recognize gastric cancer in its early or silent phase. These general examinations showed that in only 3 persons per thousand over the age of forty would cancer of the stomach be likely to occur, (Collins, Gover and Dorn, Rigler).

St. John, Swenson and Harvey (1944), among 2413 presumably healthy persons of the age of fifty without gastric complaints, found only 2 silent cancers, 1 lymphosarcoma; Dailey and Miller (1945), on x-ray examination of 500 presumably normal men over the age of forty-five, saw no cancer of the stomach. State and coworkers in the Cancer Detection Clinic of the University of Minnesota found in 1715 patients 3 cancer of the stomach (among them, one silent) 0.17 per cent. White has said that 4,000 persons must be examined in order to find one early case of gastric cancer. Therefore it was proposed to examine a selected group of

those persons who might be inclined to a higher incidence of cancer of the stomach, so-called "potential harborers of gastric cancer." Into this category fall first in order: Achlorhydria, achylia gastrica and pernicious anemia, as possible precancerous conditions. Of these three conditions, the first to merit consideration is pernicious anemia (Kaplan and Rigler). While there is no unanimous proof that there is an increase of cancer of the stomach in patients with pernicious anemia, it is undeniable that within the last fifteen to twenty years the number of patients with pernicious anemia associated with gastric cancer has risen (from 0.16 to 1.7 per cent as reported by the Mayo Clinic; Rambach's statistics the same), which brings detection of the asymptomatic stage within the range of possibility.

About thirty years ago it was not a question of pernicious anemia and cancer of the stomach, but of pernicious anemia and cancer in general. In very exact figures it was stated that really only a few cases satisfied the condition of an unquestionable combination of pernicious anemia and cancer. Heinrichsdorff (1912), in her critical review, let pass only six cases, and of these there was only one case with cancer of the stomach. Wilkinson (1933) came to the same conclusion: Pernicious anemia and malignancy of all organs show a very rare occurrence. He counts only 37 cases;

Submitted June 21, 1950.

FEBRUARY, 1951

perhaps some cases were overlooked. In the literature he found 29 cases and adds from his 370 cases with pernicious anemia 8 more of the combination with malignancy—among these only two with cancer of the

stomach; 2 uterine cancer, 1 colon cancer, 3 buccal epitheliomata. The few statistics during the time before 1933* show the rarity of the combination among living persons.

		Pernicious Anemia	Combined with Cancer	Per Cent
Giffin & Bowler	1917-1921	628	5 (1 gastric, 1 colon, 1 uterus, 1 breast, 1 esophagus)	0.16
Weinberg	1918	150	2 gastric Ca.	1.33
Levine & Ladd	1921	150	1 gastric Ca.	0.66
Panton, Maitland-Jones, Riddoch	1923	117	0 gastric Ca.	0
Conner & Birkeland	1923-1930	658	4 gastric Ca.	0.6
Murphy	1925-1928	578	4 gastric Ca. (25 of other organs)	0.7
Strandell	1931	117	4 gastric Ca.	3.4
Wilkinson	1933	378	8 (2 gastric, 1 colon, 2 uterine, 3 epitheliomata)	0.53
Deyke & Harvey	1933	52	3 gastric Ca.	5.8

From 1933 on, we have more extensive statistics about the association of pernicious anemia and cancer of the stomach. There are two kinds of statistical proof: Postmortem and living cases.

The postmortem statistics:

		No. of Autopsies	Stomach Cancer	P.A.	P. A. with Stomach Cancer
Brown	1897-1933	18,200		151	1 = 0.66 p.e.
Kaplan & Rigler	1915-1943	43,021	1010	293	36 (Also 4 Ca. of colon, rectum, caecum) = 12.3 p.e.
Kade	1919-1942	42,631	1836	229	10 = 4.3 p.e.
Lubarsch & Borchardt	1921-1927			121	2 = 1.6 p.e.
Rambach	1926-1935	11,849	641	48	6 = 12.5 p.e.
Lubarsch & Borchardt	1928-1937			95	1 = 1.05 p.e.
Coester	1928-1940		1273	149	7 = 4.7 p.e.
Strandell & Johnson	1931		3684	686	21 (5 other organs) = 3.1 p.e.
Jenner	1939			76	5 (1 extra gastric cancer) = 6.5 p.e.
Brandes	1921			22	4 = 18 p.e.

Statistical studies on living cases: (besides a great number of single cases)

		Pernicious Anemia	Combined with Stomach Cancer	Per Cent
Boettner	1921-1945	49	3	6.1
van der Sande	1927-1936	76	2	2.6
Fleischhacker & Klima	1936	200	6	3.0
Murphy & Howard	1936	440	4	0.9
Groen	1936	115	2	1.7
Roller	1936	9	1	11.0
Velde	1938	42	6	14.0
Jenner	1939	181	8	4.4
Bourne	1945-1947	15	3	20.0
Kade	1947	447	21	4.7
State & coworkers	1947	79	0	0
Kaplan & Rigler	1947	259	18	6.9
Hardt & coworkers	1948	100	1	1.0
Toelle	1949	56	5	9.0
White		16	5	31.25
Karsner	about 1000		0	0
Strauss	about 300		2	0.66
State & coworkers	1950	94 (50 new, 44 previously examined)	3	3.2

The change can be demonstrated by the follow-up of the cases of pernicious anemia and cancer of the stomach from the Mayo Clinic.

		Pernicious Anemia	Combined with Stomach Cancer	Per Cent
Giffin & Bowler	1917-1922	628	1 (4 in other organs)	0.16
Conner & Birkeland	1923-1930	658	4	0.6
Washburn & Rozendian	1931-1934	906	16 (11 new ones)	1.76
Doehring & Eusterman	1935-1939	1014	17 (14 new ones)	1.7

Rambach's statistics permits us a more exact division:

	Autopsies	Cancer of the Stomach	Pernicious Anemia	Combined
1926-1929 incl.	4618	244	19	none
1930-1935	7231	397	29	6

When we survey these statistics it is difficult to come to a conclusion. Some of them show an increase, others

*The year 1933 is chosen because important statistics go up to this year, and it is believed that from about this year on there was generally successful use of liver treatment.

do not. The high percentage can be found especially in statistics with small numbers.

Comparable are the figures by Brown, Kaplan and Rigler, Kade. Brown's go from 1897 to 1933—among 18,200 autopsies there were 151 cases of pernicious anemia and only one combination of pernicious anemia with gastric cancer—which proves the rarity of this combination at least before 1933. Kaplan and Rigler, Kade unfortunately do not give a division to enable us to compare the numbers according to liver therapy. Kaplan and Rigler saw in Minnesota among 43,021 autopsies 36 combined cases of pernicious anemia and cancer of the stomach; Kade in Germany (Hamburg) among 42,631 autopsies only 10. The percentage is 12.3 to 4.3.

The incidence is more than three times the expectation—36 combined cases instead of twelve—while Kade found a normal percentage.

It is interesting to note that Kade saw the same percentage (4.3) of cancer of the stomach among the 42,631 autopsies as among his 229 pernicious anemia cases.

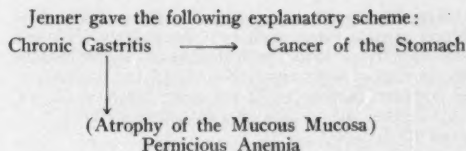
	Cancer of Stomach	Per Cent
42,631 autopsies	1836	4.3
229 pernicious anemia	10	4.3

He found the same among his living cases: 4.7 per cent.

The statistics among the living show the same differences: From 0 to 31.25 per cent. How can it be explained that Karsner did not find one case of cancer of the stomach among 1000 patients with pernicious anemia? When we add up the statistics with 100 and more cases of pernicious anemia, we have 3036 cases with pernicious anemia, among these 62 combined with cancer of the stomach (only 2.0 per cent). The authors who found the combination in a much higher percentage than could be expected by chance (Kaplan and Rigler, Jenner, Rambach, Coester, van der Sande) believe in a causal relationship between the two diseases. Washburn and Rozendaal, Bronstein, Brandes, Rhoads, Schindler, Thiele, Kade, Meythaler and Petrich, Strandell and Jansson and others hold the same point of view, while only a few (Wilkinson, Murphy, Doehring and Eusterman, Teuffl) deny any connection or are reserved in their decision.

The general belief is that there must be a causal relationship between pernicious anemia and cancer of the stomach. There is a common link in both diseases: Achlorhydria or achylia gastrica. This achlorhydria, absence of free hydrochloric acid is felt to be due to chronic gastritis leading to atrophy of the gastric mucosa. So the presence of chronic atrophic gastritis would seem to be the common basis for the development of pernicious anemia and cancer of the stomach. For pernicious anemia it was Faber, for cancer of the stomach Konjetzny, Saltzman who advocated this assumption very strongly. Knud Faber found the diffuse inflammatory process leading to destruction and atrophy of the gastric mucosa as the cause of achylia gastrica—or achlorhydria, as he calls it—which in its turn produces pernicious anemia. Konjetzny saw in 90 per cent of his cancer of the stomach cases a chronic atrophic gastritis which, in his opinion, is the predisposing factor for the development of cancer of the stomach.

FEBRUARY, 1951



We find a similar figure in Rigler, Kaplan and Fink where the atrophic gastric mucosa leads likewise to pernicious anemia and carcinoma. So it can be understood why achlorhydria, achylia gastrica and pernicious anemia are at present looked upon as precursors of cancer of the stomach. Two questions arise: 1) Is the lack of free hydrochloric acid (achlorhydria or achylia gastrica?) the same condition in pernicious anemia as in cancer of the stomach? 2) Are the pathological changes of the gastric mucosa (chronic atrophic gastritis) the same in pernicious anemia as in cancer of the stomach? In order to answer the initial questions we must first clarify the terminology.

There is a strong tendency to use the terms achlorhydria and achylia gastrica synonymously whereas a sharp distinction must be drawn between the two. It was Einhorn, in 1892, who first separated these two conditions, showing that, while achlorhydria is merely absence of free hydrochloric acid, in achylia gastrica there is no secretion at all; the gastric content is free from any juice whatsoever.

In achylia gastrica we have:

- 1) Lack of gastric secretion
- 2) Disturbance of chymification—food is undigested.
- 3) Disturbance of motility—it is increased.

Achylia gastrica is a strictly circumscribed entity; achlorhydria is a symptom, to be found in many diseases. The diagnosis of achylia gastrica should not be made by the alcohol test with histamine—that shows only lack of hydrochloric acid, but by means of the Ewald-Boas test meal which gives insight into the other functions of the stomach (the emptying time and chymification).

This entity, achylia gastrica, is constitutional and hereditary. Its development has never been observed; but it has been found up to forty years prior to the onset of pernicious anemia in which it is present in one hundred per cent. (Martius, Weinberg).

What is the case in cancer of the stomach? Here we have achlorhydria only. Some authors state that it is a constant sign, with the exception of a few cases (Maythaler and Petrich, Boettner, Rhoads). Lewis feels that it is the most important sign for the diagnosis of cancer of the stomach; but White says: The amount of free hydrochloric acid has no absolute value in the diagnosis. Actually, in cancer of the stomach, lack of hydrochloric acid occurs only in a certain percentage; all kinds of secretion can be found, from hyper- to normal and to achlorhydria.

Hartman (Among 551 cases of stomach cancer)		Mimes & Geschickter Among 339 cases
Anacidity	54 per cent	64.6 per cent
Hypoaecidity	16 per cent	35.9 per cent
Normaacidty	17.5 per cent	6.7 per cent
Hyperaacidty	4.5 per cent	—

Myre found in 9 cases of stomach cancer free hydrochloric acid in every instance. Brunschwig, Schmitz and Rasmussen found achlorhydria in approximately 60 per cent of their cases; Bloomfield and Pollard in 69 per cent; Kelling in 73 per cent; Hurst in 65 per cent; Hebbel and Gavisser after histamine stimulation in about 65 per cent.

Riegel, and Albu stated long ago that hydrochloric acid diminishes during the course of stomach cancer from normal to zero. White, too, showed that the increase of achlorhydria is concurrent with the progress of cancer: In a group of earlier cancer, achlorhydria appeared in about 50 per cent. In a group of later cancer, achlorhydria appeared in from about 75 up to 80 and 90 per cent. In the cases in which Katsch was able to make an early diagnosis so that a successful operation could be achieved, the hydrochloric acid secretion was usually maintained. Eusterman and Buerman found among 200 inoperable cases 7 per cent with free hydrochloric acid; in 200 cases which could be resected 51 per cent with free hydrochloric acid. White says much the same: The presence of free hydrochloric acid is closely related to operability. Comfort, Kelsey and Berkson examined the gastric acidity before and after the development of carcinoma of the stomach and found 150 patients whose stomachs initially contained free hydrochloric acid; 92 were given test meals at the time of the diagnosis of cancer; of these achlorhydria had developed in 39 cases (42 per cent). In the remaining 53 patients the mean free acidity of the gastric contents was only slightly lower than that of those 150 patients with free acidity at the time of the initial test meal.

In cancer of the stomach, by contrast with achylia gastrica, there is diminished expulsion time; there is no lack of secretion, but in most cases increased fluid secretion. Very often one finds highly increased combined acidity with loss of free hydrochloric acid due to lactic acid formation in pyloric obstruction.

The general belief is that chronic atrophic gastritis is common in both diseases, pernicious anemia and cancer of the stomach. Are the pathological changes of the gastric mucosa then the same? In pernicious anemia Weinberg already in 1918 first found, on examination of eleven patients with achylia gastrica who died from pernicious anemia, the following pathological changes of the stomach: There was a progressive atrophy in 8 cases, but without gastritis. These changes were localized in fundus and cardia only. In all his eleven cases the pyloric region was free from pathological changes. In three of the eleven cases the gastric mucosa was completely normal.

These findings have been confirmed in many instances. Ricker, Brown have each published one case of pernicious anemia in which the gastric mucosa was normal; Einhorn, Crohn also corroborate this evidence. Lubarsch, too, found normal or only slightly altered glands in bits of gastric mucosa washed out by means of the stomach tube; later he and Borchardt, in a record of the anatomical findings of their 121 cases of pernicious anemia from 1922 to 1927, showed that in 16.5 per cent of the cases even roughly recognizable pathological changes of the stomach did not exist. Passey saw no evidence of inflammation in a fragment of gastric mucous membrane removed during an appendectomy on a patient with pernicious anemia. Hardt,

Schwartz and Steigman found by gastroscopic examination normal gastric mucosa in 41 per cent, atrophy in 59 per cent; Schindler, Jones, Benedict and Hampton saw atrophy of the stomach not invariably present in pernicious anemia. Schiff, in 39 achylia gastrica cases, had 4 normal stomachs (gastroscopically).

The other fact—that there is no inflammatory atrophy of the pyloric region—was confirmed by Magnus and Ungley, 1938; Meulengracht, 1939; Cox, 1942.

Magnus stated that there is "non-inflammatory gastritis" in pernicious anemia, confined to the body area of the stomach and not affecting the pyloro-duodenal region; he calls it "idiopathic atrophy." Cox found the lesions in the cases of pernicious anemia different from those in so-called chronic gastritis to the extent that the changes and distribution may represent a "specific change." Hillenbrand found among his gastritis examinations one case of pernicious anemia which was quite different from his cancer cases: It showed an idiopathic non-inflammatory disease of the stomach. Today Bockus, Bank and Willard, Jones, and others express the same opinion: That there is no inflammatory process of the stomach mucosa in pernicious anemia, but an atrophic degeneration of the secretory structure. I have called the process an "inactivity atrophy." This is the only way to explain the disappearance of atrophy in patients with pernicious anemia in remission after adequate liver therapy, seen in gastroscopic examination (Schindler and Serby, Jones, Benedict and Hampton and others). The gastric mucosa becomes normal but without restoration of secretion.

The explanation of the peculiar findings—that only the cardia and fundus of the stomach show atrophic changes whereas the pylorus is free—has been given by Fox and Castle. They proved "that, in man, the important sites of secretion of the intrinsic factor are in areas containing the fundus type of glands and that the observations suggest that the source of the intrinsic factor in the human stomach coincides with the site of the degenerative process seen in histologic preparations of the stomach in pernicious anemia."

The atrophy of the gastric mucosa was not related to the length of time the disease was present, the amount of previous liver therapy, or the existing blood picture (Hardt and coworkers). This confirms the observation of Weinberg who found among his 11 patients who died of pernicious anemia different pathologic pictures, from normal gastric mucosa to slight and severe atrophy of the cardia and fundus. The idea that achylia gastrica develops on the basis of a gastritis is untenable and must be rejected; all the newer pathological findings refute it.

What are the changes of the gastric mucosa in cancer of the stomach? Mathieu, Konjetzny, Saltzman, Orator, Hurst and others have stated that a diffuse chronic gastritis accompanied by achlorhydria preceded the development of cancer of the stomach. This is a so-called "pangastritis" involving the entire mucosa (Puchert, Borchardt, Hebbel, Cox, Barker, Eusterman and others). The changes are said to be moderate in degree, "being of equal intensity throughout the stomach without regard to the location of the cancer" (Guiss and Stewart). There are, however, different findings: Torgersen saw that the changes are very often localized in the pyloric antrum where they origi-

nate and whence they spread gradually orally. Hebbel found the changes to be in greater intensity in the vicinity more immediately adjoining the carcinoma; often the more distant portions are less or not at all affected, which, in his opinion, suggested that the mucosal changes were secondary to the tumor. Magnus has even stated that the body mucosa is often normal; Hebbel, too, saw among 52 resected cancer-bearing stomachs a few in which the body mucosa were normal or nearly normal.

The comparison of the pathological changes in cancer of the stomach and in pernicious anemia shows the differences in both diseases which eliminate any connection. As has been mentioned, in gastric cancer there is a so-called "pangastritis," often gastritis in the pyloric antrum, but with normal body mucosa. In pernicious anemia we have no gastritis at all. We have degenerative changes leading to atrophy of cardia and fundus cells, without participation of the pylorus. "There is, contrary to the findings in pernicious anemia, in cancer of the stomach a singular *absence* of the widespread non-inflammatory atrophic change in the gastric mucosa which accompanies the achylia gastrica of Addison's anemia, and in no case was there a significant diminution in the total number of parietal cells. They differ fundamentally." (Magnus).

Up to this point we have only stated the differences in the pathological findings of the stomach in pernicious anemia and cancer of the stomach. Therefore the following problem is not yet solved: Is chronic atrophic gastritis with achlorhydria a precursor of gastric cancer? Borrmann, and before him Rosenheim, Matti have stressed the point that gastritis was a result rather than a cause of cancer, which seems to be confirmed by the newer findings of Hebbel.

If gastritis is supposedly the basis for the development of gastric cancer, and if it also actually *causes* achlorhydria, how can we explain the cases of stomach cancer *without* achlorhydria? It must be remembered that achlorhydria appears only in a certain percentage of gastric cancer cases where it has been observed to increase with the progress of the cancer. Nor can we readily attribute the achlorhydria to destruction of the parietal cells in the body mucosa when we have seen that in so many cases of stomach cancer the body is normal (Magnus, Hebbel).

Another question: How can we explain the development of cancer of the stomach without even gastritis (Shapiro and coworkers in 20 per cent, Hebbel), or in normal stomachs (Schindler in about 30 per cent)? We must conclude, therefore, that cancer of the stomach is possible with normal secretion and without gastritis.

Borrmann was always of the opinion that Konjetzny, in spite of his extensive work, has not given definitive proof of his statement that atrophic gastritis is a precursor of gastric cancer. Saltzman, one of the first and fiercest advocates of the gastritis theory, expresses an objective opinion by saying: "The most generally recognized belief was and is up to today that cancer of the stomach (with the exception of the ulcer-carcinomas) usually develops in healthy or not yet gastritic stomachs," and "Definitive proof in opposition to the theory of gastritis as a primary phenomenon is not yet demonstrable." But Guiss and Stewart, Hebbel, Magnus go further and conclude that, according to their extensive

pathological studies, there is no evidence whatever to support the theory that chronic atrophic gastritis can be regarded as a precancerous state.

The investigations of recent years show chronic atrophic gastritis in quite a different light. Guiss and Stewart, Hebbel have shown that an absolutely "normal" mucosa can be found only in infants, or at most during the first two decades of life. Chronic gastritis is seen in normal people of cancer age. These changes are part of the regular regressive processes which appear with increasing age and which are not necessarily of inflammatory origin. Hebbel found in 260 stomachs obtained by autopsy from individuals of all ages, dying from a variety of causes and without evidence of gastric symptoms, changes of pangastritis leading to atrophy. In Guiss and Stewart's statistics, the percentage of the gastritis in old age and in cancer of the stomach is not very different. They saw the occurrence of chronic atrophic gastritis microscopically in 97 per cent in stomachs with cancer, and in 82 per cent in stomachs of apparently normal persons who died within the cancer age. These "physiological" changes of the gastric mucosa in old age are the equivalent of gastritis in cancer of the stomach (Hillenbrand, Hamperl, Hebbel). These changes of the gastric mucosa are the same as Konjetzny saw in his cases of cancer of the stomach. This gastritis is, as Wanser emphasizes, of a benign nature.

It can be concluded that, in adults, the inflammatory infiltration of the gastric mucosa is actually to be considered "normal" (Paschke and Orator, Benedict and Mallory, Jones, Magnus, Crohn).

When the anatomical changes of the gastric mucosa are the basis for the development of cancer of the stomach, we must expect that in pernicious anemia where we have only changes in fundus and cardia of the stomach, the most likely site of cancer should be the fundus of the stomach. According to all major statistics most of the cases are localized in the pylorus (Konjetzny in 75 per cent, Welch in 60 per cent, Mimes and Geschickter in 49.8 per cent). Torgersen found out of 400 cases, 58 in pylorus and 33 in fundus (based mostly on resection). In cases of pernicious anemia with cancer he found a distinctly different proportion: Among 90 cases in the literature, where the site of the tumor could be determined, and 16 cases of his own, he found 66 cases in fundus and 33 in pylorus. His findings could support the opinion that the pathological changes in the fundus in pernicious anemia play a primary role in the development of gastric cancer.

But Guiss and Stewart say that the statistics have been largely based on series of resected stomachs, and that all the cases with cancer of cardia were considered inoperable until recently and therefore overlooked. The distribution of their series is 98 cancer cases of pylorus to 113 of the fundus (including the cardia). It reflects the extension of operability of the gastric cancer by addition of total gastrectomy and transthoracic cardiectomy. "It will be of interest to see if other new figures published will verify the suggestion that carcinomas of the pylorus and fundus occur with equal frequency."

Without question some authors have proved by the statistical method that there is an increase in the frequency of cancer of the stomach in the course of pernicious anemia. It is certain that this did not occur

in earlier years, but it can be noted in the last fifteen to twenty years since the introduction of liver therapy.

How can this increase be explained? There are two opinions:

1) Due to liver therapy in pernicious anemia there is a prolongation of life and so the patient with pernicious anemia comes into the cancer age. This view is generally accepted (Saltzman, Coester, Rambach and others). But we know that pernicious anemia generally starts at the so-called cancer age. Wilkinson found in his cases of pernicious anemia that the average age of onset in both conditions, cancer and pernicious anemia, is approximately the same. In pernicious anemia in males it was 55.9, in females, 48.6; Coester, between 53 and 71 years of age. In the literature there is only one definitive reference to prolongation of life due to liver therapy. Boettner saw that there was a five year increase in age level in his patients treated after 1930. I doubt that this slight extension of age is sufficient to explain the cancer increase. If age really plays an important role in the development of cancer of the stomach in patients with pernicious anemia, then we should find many cases of stomach cancer in achylia gastrica as the precursor of pernicious anemia. But Martius stated in 1916: "In my experience, people with achylia gastrica seldom acquire cancer of the stomach."

In the cases of achylia gastrica under my observation (about 120), I have never seen one case of cancer of the stomach, confirmed even in those followed up for twenty-five years and more; a certain number of these cases developed pernicious anemia, but no cancer of the stomach. Bloomfield and Pollard in 43 cases of achylia gastrica found no cancer of the stomach; State and coworkers saw among 350 achylia gastrica cases the development of but three cancers. Wangenstein observed among 301 cases of achylia gastrica, (to which he adds 84 cases described by Wetherby) and in 79 cases with known pernicious anemia, only three undetected cancers of the stomach.

2) The other opinion is that there is a carcinogenic agent in the liver. Teuff, Boettner have raised the issue as to whether protracted liver treatment, perhaps in too high dosages, is not entirely innocent in the increase of stomach cancer in pernicious anemia. Much experimental work supports this theory. Extracts prepared both from livers of persons who died of cancer and from non-cancerous persons produced, on subcutaneous injection into mice, malignant tumors at the site of injection (Steiner; Shabad; Kleinenberg, Neufach and Shabad; Steiner, Stanger and Bolzard and others). In experiments in which fresh liver was added to the food of tarred mice and rats, there was an acceleration in the growth of the tumor (Maisin and François, François, Caylor, Baldes and Mann, Maisin and Pourbois, Auler; Woglum saw no effect). Clinical and experimental experience shows that it is no longer doubtful that the liver contains substances which promote the growth of malignant tumors. Caspari, many years ago, strongly advocated the elimination of liver in the nutrition of patients with cancer. Of course there is no proof as yet as to whether the liver preparations we now give instead of raw liver have the same growth-producing effect as liver extract itself (Velde, Boettner).

There is, however, one very pertinent remark in the Maisin and Pourbois paper: That the anti-anemic

factor added to the diet in pure form has no influence on tar cancer development. It states further that, in contrast to the effect of liver, the dried gastric mucosa exerts an inhibiting action on tar cancer development. We know that desiccated hogs' stomachs is an effective remedy in pernicious anemia (Sharp, Sturgis and Isaacs; Ederle, Kriech and Gaensslen; Wilkinson). Is it possible that the various statistical findings with their debatable results about the development of cancer of the stomach in pernicious anemia are due to the use of different preparations?

I suggest that this can be proven only by eliminating liver preparations, and letting the human body itself do the necessary physiological work with the aid of a natural stimulant—desiccated hog's stomach. If, by this means, we supply the missing intrinsic factor so that it can combine in the stomach with the extrinsic factor, then the haematopoietic principle can be formed in the liver. We will, thereby, not only provide the necessary treatment for pernicious anemia, but at the same time eliminate any possible carcinogenic agent.

SUMMARY AND CONCLUSION

The increase in the combination of pernicious anemia and cancer of the stomach described in the last fifteen to twenty years, i.e. after the introduction of liver therapy, is in contrast to the previous rarity of this coincidence.

This increase has not been found by all observers; in fact many have found none at all.

The authors who favor the idea that there is a connection between pernicious anemia and cancer of the stomach consider chronic atrophic gastritis a common link, and that this chronic gastritis can lead to pernicious anemia or cancer of the stomach. They conclude, therefore, that chronic gastritis leading to achlorhydria or achylia gastrica is the same condition in both diseases.

But this link does not exist. In pernicious anemia we have achylia gastrica, which has nothing in common with achlorhydria but lack of hydrochloric acid. Achylia gastrica is a clinical entity with absolute lack of gastric secretion, disturbance of chymification and motility. The pathological changes are different as well: In achylia gastrica we have no gastritis; there can be normal gastric mucosa up to degenerative atrophy, so-called inactivity atrophy of the fundus and corpus glands; the pyloric region is always free from pathological changes.

In achlorhydria, as it is found in cancer of the stomach, we have pangastritis.

A comparison of these conditions shows the differences.

Pernicious Anemia	Cancer of the Stomach
Clinic: Achylia gastrica	Achlorhydria
in 100 per cent	in about 50 to 60 per cent, developing from normal to zero; increasing numbers with the progress of the disease—up to 90 per cent
Primary Condition existing before the development of pernicious anemia; inherent, constitutional; lack of secretion; disturbance of chymification; disturbance of motility (increased)	Secondary Condition often increased secretion; no disturbance of chymification; often diminished motility

Pathology: no inflammatory changes, no gastritis; mucous mucosa can be normal; degenerative atrophy of fundus and cardia pylorus free

pangastritis;
inflammatory changes,
especially on pylorus

Achylia gastrica and pernicious anemia have no connection with cancer of the stomach. They cannot be considered precancerous conditions.

It has never been proved whether chronic atrophic gastritis, which leads to achlorhydria, is primary or secondary to gastric cancer. It has been shown, however, that over 80 per cent of all persons in the cancer age have the same gastritic changes as have been found in stomach cancer; these changes are called "physiologic gastritis of old age," and cannot, therefore, be the basis for the development of malignancy.

If we eliminate gastritis as a cause, how can we explain the increase in frequency of cancer of the stomach in the course of pernicious anemia found in some statistics?

Two possible explanations have been considered: 1) the prolongation of life in pernicious anemia due to liver therapy; 2) a carcinogenic agent in the liver.

The age increase does not seem to be of importance because both diseases start at about the same age, and the prolongation of life is not sufficiently extensive to be significant.

That the development of gastric cancer may be due to a carcinogenic agent in the liver can be demonstrated only by the avoidance of liver preparations and the substitution of natural stomach preparations which contain the intrinsic factor. Thus, through the combination of the extrinsic and intrinsic factors, the haematopoietic principle can be formed by a physiological process in the liver.

BIBLIOGRAPHY

- Albu, A.: Geschwulste des Magens, einschliesslich Syphilis und Tuberkulose, in Kraus und Brugsch: Spez. Pathologie und Therapie innerer Krankheiten, Urban und Schwarzenberg, Berlin & Wien, 1921, Vol. V, p. 911.
- Auler, H.: Ernährung und Krebs. Die Ernährung, 1:150, 1936.
- Barker, L. F.: The Etiology and Treatment of Pernicious Anemia, J. A. M. A., 87:80, 1926.
- Benedict, E. B. and Mallory, T. B.: Correlation of Gastroscopic and Pathological Findings in Gastritis, Surg. Gyn. and Obst., 76:129, 1943.
- Bloomfield, A. L. and Pollard, W. S.: Gastric Anacidity, 1933, The Macmillan Co., New York.
- Bockus, H. L., Bank, J. and Willard, J. H.: Achlorhydria with a Review of 210 Cases in Patients with Gastrointestinal Complaints, Am. J. Med. Sci., 184:183, 1932.
- Borchardt, H.: Ueber das Verhalten der Magenschleimhaut beim Carcinoma Ventriculi, beim Ulcus Ventriculi und beim Carcinoma ex Ulcere, Virchows Arch. Path. Anatomie, 275: 790, 1929.
- Bormann, R.: Geschwulste des Magens und Duodenums, in Henke, F. and Lubarsch, O.: Handb. der Spez. Pathologischen Anatomie und Histologie, Berlin, J. Springer, Vol. IV, pt. 1, p. 855, 1926.
- Boettner, H.: Magenkarzinom bei Perniziöser Anämie, Med. Kl., 41: 571, 1946.
- Bourne, W. A.: Cancer of the Stomach in Addison's Anemia, Brit. Med. J., 1:92, 1948.
- Brandes, Th.: Ueber die Beziehungen der Perniziösen Anämie zum Magenkarzinom, Med. Klin., 17:193, 1921.
- Brønstein, L. H.: Carcinoma of Stomach Developing in Pernicious Anemia, J. Lab. Clin. Med., 28:44, 1942.
- Brown, M. R.: The Pathology of the Gastro-intestinal Tract in Pernicious Anemia, in Subacute Combined Degeneration of the Spinal Cord, New Engl. J. Med., 210:473, 1934.
- Brunschwig, A., Schmitz, R. L. and Rasmussen, R.: Experimental Observations on Achlorhydria of Gastric Cancer, J. Nat. Cancer Inst., 1:481, 1941.
- Caspari, W.: Ueber den Einfluss der Kost auf das Wachstum von Impfgeschwulsten, Z. f. Krebsforschung, 43:255, 1935.
- Caylor, H. D., Boides, E. J. and Mann, F. C.: Flexner-Jobling Rat Carcinoma: Effect of Feeding Liver and Muscle on Growth of Tumor, Arch. Path., 11:854, 1931.
- Collins, S. D., Gover, M. and Dorn, H. F.: Trend and Geographic Variation in Cancer Mortality and Prevalence, with Special Reference to Gastric Cancer, J. Nat. Cancer Inst., 1:425, 1941.
- Comfort, M. W., Kelsey, M. P. and Berkson, J.: Gastric Acidity Before and After the Development of Carcinoma of the Stomach, J. Nat. Cancer Inst., 7:37, 1947.
- Conner, H. M. and Birkeland, J. W.: Coexistence of Pernicious Anemia and Lesions of Gastrointestinal Tract, I. Carcinoma of the Stomach, Ann. of Int. Med., 7:89, 1933.
- Coester, E.: Magenkrebs nach Perniziöser Anämie, Frankfurter Zeitsch. Pathologie, 55:269, 1941.
- Cox, A. J.: The Stomach in Pernicious Anemia, Am. J. Path., 19:491, 1943.
- Crohn, B. B.: Chronic Gastritis: Clinical Aspects, Bull. N. Y. Acad. Med., 13:392, 1939.
- Crohn, B. B.: Achlorhydria: Its Ultimate Significance, Tr. Ass. Life Ins. Div. America, 28:74, 1942.
- Dailey, M. E. and Miller, E. R.: Research for Symptomless Gastric Cancer in Five Hundred Apparently Healthy Men of Forty-five and Over, Gastroenterology, 5:1, 1945.
- Doehring, P. C. and Eusterman, G. B.: Association of Pernicious Anemia and Carcinoma of the Stomach, Arch. Surg., 45:554, 1942.
- Dyke, S. C. and Harvey, E.: The Efficient Treatment of Pernicious Anemia, Lancet, 2:59, 1933.
- Ederle, W., Kriech, H. and Gansslen, M.: Behandlung der Anämia Perniciosa mit Injiziertem Magenextrakt, Klin. Wch., 10:313, 1931.
- Einhorn, M.: On Achylia Gastrica, Med. Record, 41:650, 1892.
- Einhorn, M.: Diseases of the Stomach, Wm. Wood Co., 7th Ed., N. Y., 1929.
- Eusterman, G. B.: The Gastritis Problem: Notes on Histologically Verified Cases, South. Med. J., 29:685, 1936.
- Eusterman and Bucerman: quoted by White.
- Faber, K.: Gastritis and Its Consequences, Oxford Univ. Press, London, 1935, p. 119.
- Fleischhacker, H. and Klima, R.: Die Anämien nach Magen- und Darmoperationen, 129:226, 1936.
- Fox, H. J. and Castle, W. A.: Observations on Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: Differences in Site of Secretion of Intrinsic Factor in Hog and in Human Stomach, Am. J. Med. Sci., 203:18, 1942.
- Francois, M.-A.: L'influence du Regime Alimentaire sur le Comportement du Cancer au Goudron sur la Souris Blanche, Cancer, Bruxelles, 8:1, 1931.
- Giffin, H. Z. and Bowler, J. P.: Diseases which may be Associated with Pernicious Anemia, Minn. Med., 6:13, 1922.
- Groen, J. J.: Clinical and Experimental Studies on Pernicious Anemia and Secondary Deficiency, Scheltila & Holkem, Amsterdam, 1936.
- Guis, L. W. and Stewart, F. W.: Chronic Atrophic Gastritis and Cancer of the Stomach, Arch. Surg., 46:823, 1943.
- Guis, L. W. and Stewart, F. W.: Distribution of Gastric Changes Accompanying Gastric Cancer in Various Locations, Arch. Surg., 57:624, 1948.
- Hampel, H.: Ueber Akute Gastritis, Wiener Kl. Wch., 45:515, 1932.
- Hardt, L. L., Schwartz, S. O. and Stiegman, F.: Gastroscopic Observations in Pernicious Anemia, Gastroenterology, 10:108, 1948.
- Hartman, R. H.: The Prevalence of Free Hydrochloric Acid in Cases of Carcinoma of the Stomach, Am. J. Med. Sci., 163:186, 1922.
- Hebbel, R. and Gaviar, D.: The Relationship Between Gross Type of Gastric Carcinoma and Anacidity, Surgery, 24:512, 1940.
- Hebbel, R.: Gastric Gastritis, Its Relation to Gastric and Duodenal Ulcer and to Gastric Carcinoma, Am. J. Path., 19:43, 1943.
- Heinrichsdorff, A.: Ueber die Beziehungen der Perniziösen Anämie zum Karzinom, Fol. Haemat., 14:359, 1912.
- Hillenbrand, K.: Histopathologische und Histologische Untersuchungen Ueber die soz. Chronische Gastritis, Beitr. z. Path. Anatomie und z. Allg. Path., 85:1, 1930.
- Hurst, A. F.: Precursors of Carcinoma of the Stomach, Lancet, 2:1023, 1929.
- Hurst, A. F.: Cancer of the Alimentary Tract, Lancet, 1:553, 1939.
- Jenner, A. W. F.: Perniziöse Anämie und Magenkarzinom, Act. Med. Scand., 102:529, 1939.
- Jones, C. M., Benedict, E. B. and Hampton, O. H.: Variations in the Gastric Mucosa in Pernicious Anemia: Gastroscopic, Surgical and Roentgenological Observations, Am. J. Med. Sci., 190:596, 1935.
- Jones, Ch. M.: Clinical Evaluation of Gastritis, Am. J. Dig. Dis., 8:205, 1941.
- Kade, H.: Perniziöse Anämie in Kindesalter, Zeitschr. Kinderh., 65:47, 1947.
- Kade, H.: Die Notwendigkeit und Aufgabe der Perniziösen-Beratungsstellen fuer die Früherfassung des Magenkrebses, Med. Klin., 42: 329, No. 8, 1947.
- Kaplan, H. S. and Rigler, L. G.: Pernicious Anemia and Carcinoma of the Stomach: Autopsy Studies Concerning Their Interrelationship, Am. J. Med. Sci., 209:339, 1945.
- Kaplan, H. S. and Rigler, L. G.: Pernicious Anemia and Susceptibility to Gastric Neoplasia, I. Lab. and Clin. Med., 32:644, 1947.
- Karsner: quoted by White.
- Katseh, G.: Krankheiten des Magens, Bergmann und Stehelin, Handbuch der Inneren Medizin, Vol. 3, p. 401, Berlin, J. Springer, 1938.
- Kellings, G.: Stützvisites ueber Salzaeuereuerung im Magen, Arch. Verdauungskr., 15:568, 1909.
- Kleinenberg, H. E., Neufach, S. A. and Shabad, L. M.: Endogenic Blastogenic Substances, A. J. Cancer, 39:461, 1940.
- Kleinenberg, H. E., Neufach, S. A. and Shabad, L. M.: Further Study of Blastogenic Substances in the Human Body, Cancer Research, 1:853, 1941.
- Konietzky, G. E.: Ueber die Beziehungen der Chronischen Gastritis mit ihren Folgeerscheinungen und des Chronischen Magencancers zur Entwicklung des Magenkrebses, Beitr. Klin. Chirurgie, 1:455, 1913.
- Konietzky, G. E.: Entzündungen des Magens in Henke, F. and Lubarsch, O.: Handbuch der Speziellen Pathologischen Anatomie und Histologie, Berlin, J. Springer, 4:2768, 1928.
- Levine, S. A. and Ladd, W. S.: Pernicious Anemia: A Clinical Study of One Hundred and Fifty Consecutive Cases with Special Reference to Gastric Acidity, 32:254, 1921.
- Lewis, D.: Carcinoma of the Stomach, Brit. Med. J., 33:589, 1930.
- Lubarsch, O.: in Martius, F.: Achylia Gastrica, 1897.
- Lubarsch, O. and Borchardt, H.: Atrophie und Sogenannte Degeneration des Magens und Darmes, Henke und Lubarsch, Handb. d. Speziellen Pathologischen Anatomie und Histologie, 4:311, 1929.
- Magnus, H. A.: The Pathology of Simple Gastritis, J. Path. and Bact., 58:375, 1946.
- Magnus, H. A. and Unley, C. C.: Gastric Lesion in Pernicious Anemia, Lancet, 1:420, 1938.
- Maisin, I. et Francois, M.-A.: Influence du Regime Alimentaire sur l'Ecllosion et l'Evolution du Cancer du Goudron, Ann. de Med., 24:455, 1928.

- Maisin, J. et Pourbois, Y.: Growth-promoting and Growth-inhibiting Substances Extracted from Organs, *Am. J. Cancer*, 24:357, 1935.
- Martius, F.: Achylia Gastrica, ihre Ursachen und ihre Folgen mit einem Anatomischen Beitrag von O. Lubarsch, Leipzig und Wien, 1897, F. Deuticke.
- Martius, F.: Achylia Gastrica und Perniciöse Anämie, *Med. Klin. No.* 18:481, 1916.
- Mathieu, A.: Etat de la Muqueuse de l'Estomac dans le Cancer de cet Organ, *Arch. Gen. de Med.*, 1:402, 371, 1889.
- Matti, H.: Beitrag zur Kenntnis des Magenkarzinoms. Untersuchungen ueber die Ursachen des Veränderten Chemismus bei Fäulen von Magenkrebs, *Deutsche Zeitschr. Chirurgie*, 104:425, 1910.
- Meulenbracht, E.: Histologic Investigation into Pyloric Gland Organ in Pernicious Anemia, *Am. J. Med. Sci.*, 197:201, 1939.
- Meythaler, F. and Petrich, H.: Perniciöse Anämie und Magenkarzinom, *Kl. Ws.*, 17:196, 1938.
- Mimes, J. F. and Geschickter, Ch. F.: Some Clinical Features of Carcinoma of the Stomach, *Am. J. Cancer*, 27:740, 1936.
- Murphy, W. P.: Anemia in Practice, W. B. Saunders, Phila. and London, 1939, p. 215.
- Murphy, W. P.: Twenty Years of Liver Therapy, *Blood*, 3:32, 1948.
- Murphy, W. P. and Howard, J.: An Analysis of the Complications Occurring in a Series of Patients with Pernicious Anemia, *Rev. Gastroent.*, 3:98, 1936.
- Myhre, H.: On the Significance of Large Niche in the Stomach, *Act. Rad.*, 22:482, 1941.
- Orator, V.: Beitrage zur Magenpathologie IV. Klinischer Teil, *Arch. Klin. Chirurgie*, 134:663, 1925.
- Panton, P. N., Maitland-Jones, A. G. and Riddoch, G.: Pernicious Anemia: An Analysis of 117 Cases, *Lancet*, 1:274, 1923.
- Paschalis, K. and Orator, V.: Beitrage zur normal Histologie des Menschlichen Magens, *Zeitschr. Anatomie und Entwicklungs-g.*, 67:494, 1923.
- Passer, R. M.: The Gastric Mucous Membrane in Addison's Anemia, *Guy's Hosp. Report*, 72:172, 1922.
- Puchert, H.: Ueber die Magenschleimhaut bei Geschwuer und bei Krebs, mit Berücksichtigung des Lymphatischen Gewebes, *Virchows Arch. Path. Anatomie*, 280:385, 1931.
- Rambach, H.: Ueber die Entwicklung von Magenkrebs bei der Perniciösen Anämie, *Monatschr. fuer Krebsbekämpfung*, 4:201, 1936.
- Ricker, J.: Ueber die Beziehungen der Achylie zur Perniciösen Anämie, *Med. Kl.*, 1:8, 1904.
- Riegel, F.: Die Erkrankungen des Magens, *Nothnagels Spez. Pathologie und Therapie*, Hoelder, Wien, Vol. XVI, p. 2, 1897.
- Rigler, L. G.: Roentgen Examination of the Stomach in Symptomatic Persons, *J. A. M. A.*, 137:1501, 1948.
- Rigler, L. G., Kaplan, H. S. and Fink, D. L.: Pernicious Anemia and the Early Diagnosis of Tumors of the Stomach, *J. A. M. A.*, 128: 426, 1945.
- Rhoads, C. P.: Gastric Cancer as a Sequel to Gastritis, Particularly the Gastritis of Pernicious Anemia, *J. Nat. Cancer Inst.*, 1:311, 1941.
- Roller, E.: Anemia Perniciosa and Carcinom, *Mitt. Ges. innere Medizin in Wien, Sitzung*, April 30, 1936; *Kl. Ws.*, 2:1623, 1936.
- Rosenheim, Th.: Ueber Atrophische Prozesse an der Magenschleimhaut in Ihren Beziehungen zum Carcinoma als selbständige Erkrankung, *Berlin Kl. Ws.*, 25:1021, 1888.
- Saltzman, G. F.: Studien Ueber Magenkrebs mit besonderer Berücksichtigung der Schleimhautveränderungen, *Arch. Path. Institut der Universitat Helsingfors*, Vol. I, Jena G. Fischer, 1913.
- Saltzman, G. F.: Perniciöse Anämie und Karzinom, *Act. Med. Scand.*, 75:198, 1931.
- Schiff, J.: Discussion of Rhoads, C. P., p. 519.
- Schindler, R.: Early Diagnosis of Cancer of the Stomach; Gastroscopy and Gastric Biopsies, *Gastrophotography and X-rays*, *J. Nat. Cancer Inst.*, 1:451, 1941.
- Schindler, R., Nutter, V. B., Groon, H. E. and Palmer, W. L.: Anatomic Foundation of Anacidity; A Gastroscopic Study, *Arch. Int. Med.*, 66:1060, 1940.
- Schindler, R.: Discussion of Rhoads.
- Schindler, R. and Serby, A. M.: Gastroscopic Observations in Pernicious Anemia, *Arch. Int. Med.*, 63:334, 1939.
- Shabad, L. M.: Production Experimentale de Tumeurs Malignes par un Extrait Benzenique du Foie d'un cancerux, *A. Propos de la Question de Substances Cancerigenes*, *Compt. Rend. Soc. de Biol.*, 124:213, 1937.
- Shapiro, N., Schiff, L., Maher, M. M. and Zimninger, M. M.: Some Observations on Atrophic Gastritis and Gastric Cancer, *J. Nat. Cancer Inst.*, 2:583, 1942.
- Sharp, E. A.: An Antianemic Factor in Desiccated Stomach, *J. A. M. A.*, 93:749, 1929.
- St. John, F. B., Swenson, P. C. and Harvey, H. D.: Experiment in Early Diagnosis of Gastric Carcinoma, *Ann. Surg.*, 119:225, 1944.
- State, D., Givner, D., Hubbard, B. T. and Wangenstein, O. H.: Gastric Cancer, *J. A. M. A.*, 142:1128, 1950.
- State, D., Moore, G. and Wangenstein, O. H.: Carcinoma of the Stomach, *J. A. M. A.*, 135:262, 1947.
- State, D., Varco, L. and Wangenstein, O. H.: An Attempt to Identify Likely Precursors of Gastric Cancer, *J. Nat. Cancer Inst.*, 7:379, 1947.
- Steiner, P. E.: A Cancerogenic Tissue Extract from Human Sources, *Science*, 92:431, 1940.
- Steiner, P. E.: The Incidence of a Carcinogenic Factor in the Liver of Cancer, Noncancer, Cirrhotic and Negro Patients, *Cancer Research*, 3:385, 1943.
- Steiner, P. E., Stanger, D. W. and Bolzard, M. N.: Comparison of Carcinogenic Activity in Extracts of Human Liver and Other Human and Animal Organs, *Cancer Research*, 7:273, 1947.
- Strander, B. and Jansson, T.: Anemia Perniciosa och Cancer, *Nordisk Medicinsk Tidskrift*, 14:1316, 1931.
- Strauss, M. B.: quoted by White.
- Sturgis, C. C. and Isaacs, R.: Desiccated Stomach in the Treatment of Pernicious Anemia, *J. A. M. A.*, 93:747, 1929.
- Teuffl, R.: Perniciöse Anämie und Magenkarzinom, *Arch. Verdauungs-kr.*, 61:166, 1937.
- Thiele, W.: Perniciöse Anämie und Magenkarzinom unter besonderer Berücksichtigung ihres Familiären Auftretens, *Klin. Ws.*, 15:921, 1936, No. 26.
- Toelle, H.: Perniciöse Anämie und Magenkarzinom, *Deutsche Med. Ws.*, 74:604, 1949.
- Torgerson, J.: Localization of Gastritis and Gastric Cancer, Especially in Cases of Pernicious Anemia, *Acta Radiol.*, 25:845, 1944.
- van der Sande, D.: Question of Relation Between Pernicious Anemia and Gastric Cancer, *Nederlandsch Tijdschr. v. Geneesk.*, 80:4774, 1936.
- Velde, G.: Die Beziehungen zwischen Perniciöser Anämie, Magenpolypen und Magenkarzinom, *Zeitschr. Kl. Med.*, 134:653, 1938.
- Wangenstein, O. H.: The Problem of Gastric Cancer, *J. A. M. A.*, 134:1161, 1947.
- Wanner, R.: Die Banale Chronische Gastritis und Ihre Beziehungen zum Magenkarzinom, *Beitr. Path. Anat. und Allg. Path.*, 103:113, 1939.
- Washburn, R. N. and Rosendaal, H. M.: Gastric Lesions Associated with Pernicious Anemia, *Ann. of Int. Med.*, 11:2172, 1938.
- Weinberg, F.: Karzinom und Perniciöse Anämie, *Zeitschr. Klin. Med.*, 85:392, 1918.
- Weinberg, F.: Achylia Gastrica und Perniciöse Anämie, *D. Arch. Kl. Med.*, 126:447, 1918.
- Weinberg, F. S.: The Prevention of Macrocytic Achylic Anemia (Addison's Pernicious Anemia), *Proc. Rudolph Virchow Med. Soc. in City of N. Y.*, 5:8, 1946.
- Welch: quoted by White.
- Wetherby, M.: Gastric Achlorhydria: A Clinical and Gastroscopic Study, *Univ. Minnesota Hosp. Bull.*, 12:473, 1941.
- White, F. W.: Tumors of the Stomach and Small Intestine, *Nelson Medicine 5*, page 295, Thomas Nelson & Sons, 1946.
- Wilkinson, J. F.: Pernicious Anemia and Malignant Disease, *Act. Med. Scand.*, 80:466, 1933.
- Wilkinson, J. F.: The Relationship Between the Anti-anemic Principles in Stomach and Liver, *Lancet*, 2:629, 1933.
- Woglum, W. H.: Liver Diet and Tumor Growth, *Am. J. Cancer*, 16:364, 1932.

COMPLICATIONS OF CHRONIC ULCERATIVE COLITIS

MERTON L. BOWN, M. D., ANTHONY M. KASICH, M. D., AND BERTHOLD WEINGARTEN, M. D., New York, N. Y.

IN THE 24 YEAR period from 1925 to 1949 inclusive, there have been treated at Montefiore Hospital, 147 cases of ulcerative colitis. Most of these have been of more than ordinary severity and duration. In reviewing our experience with these patients, we have been impressed by the unusual number and seriousness of complications, greater than that usually reported (1). Since a knowledge of the nature and incidence of complications is of such great importance in the course, treatment and prognosis of this disease, we have considered it worth while to list and discuss briefly the complications in this severely ill group.

Our series includes all patients with ulcerative colitis who were admitted to Montefiore Hospital from 1925 to 1949 inclusive. In this group of patients, many of

Medial Division, Montefiore Hospital, New York, N. Y.

Submitted May 12, 1950.

TABLE I. AGE OF ONSET OF ULCERATIVE COLITIS

Decade	Number of cases
1-9	3
10-19	45
20-29	49
30-39	22
40-49	14
50-59	7
60-69	7
70-79	1
80-89	1
Total	147

whom had had the disease for more than fifteen years there were 83 males and 64 females. As shown in Table 1, ninety-four or 63.2 per cent first became ill between the ages of ten and thirty years. The number and percentages of complications are listed in Table 2. It will be noted

TABLE II. INCIDENCE OF COMPLICATIONS IN SEVERE CHRONIC ULCERATIVE COLITIS

Complication	Number	Percentage
Stricture of the Colon	27	18.4
Perirectal Abscess or Fistula	27	18.4
Intestinal Obstruction	25	17.0
Clubbing of Fingers or Toes	24	16.3
Perforation of Colon	23	15.6
Cardiac Involvement	23	15.6
Liver Involvement	22	15.0
Polyposis	22	15.0
Infantilism	21	14.3
Nutritional Edema	20	13.6
Skin Manifestations	17	11.6
Renal Insufficiency	12	8.2
Arthritis	11	7.5
Malignant Degeneration	7	4.8
Rectovaginal Fistula	5	3.4
Fistula of the Abdominal Wall	5	3.4
Pleural Effusion	3	2.0
Subdiaphragmatic Abscess	2	1.4
Liver Abscess	1	0.7
Gastrocolic Fistula	1	0.7
Ascites	1	0.7
Thrombosis of Renal Veins	1	0.7
Amyloidosis	1	0.7

that both the number and the seriousness of the complications are greater than usually reported, a fact explained by the advanced nature of the disease in most of these patients. Forty-nine of the patients are known to be dead and 45 are still under treatment. The number deceased is undoubtedly higher, for we have been unable to trace 53 patients.

TABLE III. MORTALITY IN 147 CASES OF SEVERE ULCERATIVE COLITIS

	Number of Cases	Percentage of Total
Dead	49	33.3
Under Treatment	45	30.6
Not Traced	53	36.1
Total	147	100

DISCUSSION OF THE MORE IMPORTANT COMPLICATIONS

Stricture and Obstruction.—In this group there were 27 cases of stricture of the colon, twenty-five of which went on to obstruction. The strictures, which may occur anywhere in the large bowel, are most common in the rectum (2). The inflammatory destruction and repair of the wall, which cause narrowing and shortening and the "gas-pipe" appearance typical of chronic ulcerative colitis, are also responsible for the strictures. With progression of the disease, the lumen may narrow to a point where passage of feces is impeded and complete obstruction results.

Rectal Lesions.—Fistulas and perirectal abscesses occurred in 27 cases. Fistulas usually have their internal openings in one of the crypts of Morgagni, and at these points ragged ulcers up to 1 cm. in diameter may be seen. Perirectal abscesses with extensive destruction of tissue often involve several of the perianal spaces (3). There is little protective reaction around these lesions and large sloughs, frequently involving the external anal sphincter, causing deformity of the anus often with incontinence. Anal ulcers, solitary or multiple, were seen in some of our cases. Perianal lesions at times make the patient so miserable and are so refractory to treatment that only by an ileostomy can

relief be obtained. Hemorrhoids are extremely common, the cause of much discomfort, and may be sources of severe hemorrhage.

Perforation of the Bowel.—There were 23 cases of perforation of the bowel, with 17 deaths. Perforations about the rectum below the peritoneal fold are usually walled off, though in women the abscess occasionally ruptures into the vagina causing a rectovaginal fistula. This occurred in five of our patients. In one of the cases the fistulous tract resulted from the invasion of the vagina by a carcinoma arising in the rectum. Perforations above the rectum are grave, resulting in generalized peritonitis. Perforations as a rule occur in acute fulminating cases or during acute exacerbations of chronic cases, though they may take place when the disease seems quiescent. That perforation may occur even in defunctionalized colons after ileostomy is often forgotten (4).

Perforation may take place anywhere in the colon, and the terminal ileum is involved, in about 25 per cent of cases of severe ulcerative colitis. In six of our cases the perforation was in the ileum alone, and in three other cases the ileum was perforated together with the ascending colon, transverse colon and the sigmoid. In one case perforations occurred simultaneously in the ileum, sigmoid and the rectum. In three cases the cecum was involved, twice with the rectum; in four cases the transverse colon was perforated, once with the descending colon. In two cases the perforation was in the sigmoid and in four others it was limited to the rectum. In one case the entire colon was perforated in numerous places.

Liver Involvement.—In 22 cases there was evidence of liver dysfunction, as determined by bromsulphalein retention, thymol turbidity and cephalin flocculation tests, prothrombin studies, and urinary urobilinogen determinations. Eight patients showed clinical jaundice. In one case an abscess of the liver was discovered on autopsy. In none of our cases was actual cirrhosis encountered.

Polyposis.—Polyps were seen in 22 cases of our group. The polyps developing in ulcerative colitis are not true adenomas, but rather pseudopolyps. They result when repeated attacks of inflammation leave small ragged islands of mucosa which become infiltrated with fibrous tissue and assume a polypoid appearance (5). Whether these pseudopolyps can develop into adenomatous polyps, as is believed by many gastroenterologists, has been the subject of lively debate. The subject is of more than academic importance, for true polyps are generally recognized by pathologists to be prone to malignant degeneration.

Malignant Degeneration.—There were seven cases of carcinoma in this group, an incidence of 4.8 per cent (6). In four instances the cancer occurred in the rectum, twice in the transverse colon, and once in the terminal ileum. In all cases the neoplasm was single. Carcinoma usually occurs in long standing cases and five of the patients in whom it developed had had ulcerative colitis twelve to eighteen years before the onset of malignancy. The occurrence of three cases of cancer in defunctionalized colons after ileostomy, emphasizes once again the important fact that diversion of the fecal stream is no guarantee against progression of the disease. All of these patients died, for as usual in these cases, even palliative surgery was impossible.

There is general agreement among clinicians that cancer of the bowel occurring in a patient with ulcerative colitis is somehow related to the colitis, although to pathologists this correlation is not always so clear cut (7). There are several reasons for this. When cancer is discovered in a patient with ulcerative colitis, it usually occurs at the same sites as when it arises independent of the colitis, and since cancer of the colon is a relatively common disease the occurrence of the two lesions in the same patient may be coincidental. It should also be noted that ulceration of the colon, at times indistinguishable from ulcerative colitis, may be found in cancer of the colon, especially above the lesion in cases of obstruction. There is also the fact that, especially in specimens taken for biopsy, a diagnosis of malignancy cannot always be made with definiteness, for areas of epithelial regeneration, actually representing inflammatory hyperplasia, may be erroneously interpreted by the pathologist as carcinoma. While there would seem little reason to doubt that in cases of young individuals with ulcerative colitis who develop cancer, the colitis is etiologically related to the carcinoma, it is equally clear that in other cases the co-existence of the two lesions may be fortuitous.

Renal Insufficiency.—Involvement of the kidneys is not rare in ulcerative colitis and occurred in 12 of our patients. The finding of albumin, red blood cells, and the casts in the urine; abnormal values for urea clearance, concentration and dilution tests, and elevation of blood urea and non-protein nitrogen were the criteria used in determining the presence of disease of the kidneys. Kidney damage is seldom severe enough to be the direct cause of death in these patients, though it undoubtedly contributes to it.

Skin Manifestations.—In 17 patients there were notable lesions in the skin. As a rule the skin is involved only in severe, active cases. Elevated, tender nodules similar to erythema nodosum ulcers form on the skin of the legs, without any evidence of infection. These are extremely refractory to local treatment. In some cases these nodules show central area of necrosis, and by coalescence form large destructive ulcers, the floor of which is formed by muscle or fascia. These ulcers, which have been likened by Felsen (8) to those caused by B. histolyticus, where massive necrosis and dissolution occur overnight, are extremely refractory to treatment and healing results only when the colitis has been brought under control. The breaking down of the skin is primarily due to the depleted condition of the patient, and only when the anemia, the hypoproteinemia, and other nutritive and vitamin imbalances are corrected, will the ulcers respond to treatment (9).

Arthritis.—Eleven of our patients were reported as having arthritis. In some of these there was definite effusion into the joints. Purulent effusions may occur.

In others, the arthritis was of the osteohypertrophic variety and undoubtedly was a coincidental finding.

Miscellaneous Complications.—Severe malnutrition and high grades of anemia are so common that they are really a part of the disease. Clubbing of the fingers was rather common, occurring in 24 patients. Twenty-one patients showed evidence of infantilism, manifested by underdevelopment of the skeleton and retardation of the secondary sex characteristics. Edema of the extremities with hypoproteinemia, was seen in 20 patients. Three patients had pleural effusion, with no apparent cause; two had subdiaphragmatic abscess, and one each had gastrocolic fistula, liver abscess, bilateral thrombosis of the renal veins, and amyloidosis of the kidneys, liver and spleen.

SUMMARY AND CONCLUSIONS

1. Complications of ulcerative colitis are an important factor in the morbidity and mortality of the disease. In 147 patients with severe ulcerative colitis observed at Montefiore Hospital over a 25 year period, few were without some complication.

2. The frequency and gravity of complications are dependent upon the duration and severity of the colitis.

3. Among the major complications encountered were: Stricture of the colon, 27 (18.4 per cent); intestinal obstruction, 25 (17.0 per cent); perirectal abscess and/or fistula, 27 (18.4 per cent); perforation of the bowel, 23 (15.6 per cent); liver involvement, 22 (15.0 per cent); polyposis, 22 (15.0 per cent); skin manifestations, 17 (11.6 per cent); malignant degeneration, 7 (4.8 per cent).

4. In the miscellaneous group of less serious complications may be mentioned: Clubbing of the fingers, 24 (16.3 per cent); infantilism, 21 (14.3 per cent); nutritional edema, 20 (13.8 per cent); arthritis, 11 (7.5 per cent); renal insufficiency, 12 (8.2 per cent); recto-vaginal fistulas, 5 (3.4 per cent); pleural effusion, 3 (2.0 per cent); gastrocolic fistula, liver abscess, ascites, bilateral thrombosis of the renal veins, and amyloidosis of the kidneys, liver and spleen, 1 each (0.7 per cent).

REFERENCES

1. Ricketts, W. E. and Palmer, W. L.: *Gastroenterology*, 7: 55, 1946.
2. Lund, F. B.: *N. England J. Med.*, 206:156, 1932.
3. Smith, N. D., Jackman, R. J.: *Surgery*, 7:69, 1940.
4. Ferguson, L. K., and Stevens, L. W.: *Gastroenterology*, 11:640, 1948.
5. Barger, J. A., and Sauer, W. G.: *Clinics*, 3:516, 1944.
6. Kasich, A. M., Weingarten, B., and Brown, M. L.: *Clin. N. America*, 1421-1437, Sept. 1949.
7. Willis, R. A.: *Pathology of Tumors*, London Butterworth & Co., 1948.
8. Felsen, J.: *N. Y. State J. Med.*, 41:2228, 1941.
9. Kantor, J. L., and Kasich, A. M.: *Handbook of Digestive Diseases*, Ed. 2, St. Louis, Mo., The C. V. Mosby Co., 1949.

AN APPRAISAL OF THE PSYCHOLOGICAL RELATIONSHIP OF CORONARY DISEASE TO PEPTIC ULCER*

MAURICE FELDMAN, M. D. AND SAMUEL MORRISON, M. D., Baltimore, Md.

THERE SEEMINGLY appears to be, in some respects, a psychological similarity in the relationship between the clinical aspects of coronary occlusion and peptic ulceration. The purpose of this paper, therefore, is to determine whether or not such a relationship actually exists. The first part of this study was undertaken to determine the correlation and association of peptic ulcer and coronary occlusion, by means of an autopsy study. There has been very little written on the subject of this relationship, even though it is well known that gastrointestinal symptoms are common manifestations of the clinical picture of coronary disease. In recent years there has been considerable literature on the relationship of gall bladder disease and hiatus hernia with coronary disease. It is our desire to investigate the relationship of coronary occlusion and peptic ulceration in more detail, comparing the two conditions from an anatomic-pathological as well as from a clinical point of view.

For the purpose of this study a survey was made of 1,522 autopsies at the Sinai Hospital, to determine, if possible, the true anatomical incidence and relationship between these two conditions. Among the 1,522 consecutive autopsies, of all ages from infancy to old age, there were 101 cases of peptic ulcer or an incidence of 6.6 per cent. In this autopsy material, 753 cases of all types and degrees of coronary disease were found. These ranged from minimal microscopic to marked gross changes of the coronary vessels. This incidence of coronary pathology seemed, at first sight, to be exceedingly high. However, this can be explained by the fact that the blood vessels of the heart were minutely examined in this series of autopsies.

Among the 753 cases of varying stages of arteriosclerosis of the coronary arteries, there were 152 cases with coronary occlusion, an incidence of 20 per cent. Of the 753 cases, there were 68 with peptic ulcer, an incidence of 9 per cent. Of the 152 cases of coronary occlusion, peptic ulcer was present in sixteen or an incidence of 10.5 per cent. Whereas the general autopsy incidence of peptic ulcer is between 1 and 5 per cent, the higher incidence noted among coronary disease patients was a stimulus to investigate this problem further. It seemed to us that in some aspects of the two conditions, there is an apparent clinical relationship in many ways. According to our autopsy findings, the incidence of peptic ulcer seemed to be only slightly greater than in the general autopsied population. On the other hand, others who have studied this problem have shown that there is no relationship whatever between the two conditions. Walsh et al. in 1,000 patients with clinical coronary disease found peptic ulcers in twenty-seven or 2.7 per cent. In 2,737 autopsies in persons over the age of 20 years they found 149 cases of peptic ulcer or an incidence of 5 per cent.

*We wish to express our grateful appreciation to Dr. Tobias Weinberg, for the privilege to use the autopsy material from the Department of Laboratories of the Sinai Hospital.

Submitted May 5, 1950.

Among these autopsies there were 576 cases which revealed evidence of coronary disease and of these there were thirty cases of peptic ulcer or an incidence of 5 per cent. Their findings therefore showed the incidence of peptic ulcer occurred with equal frequency in patients without coronary disease. Boas, in discussing Walsh's paper, pointed out that one must not conclude that there is never any relationship between peptic ulcer and coronary disease but recognize that further intensive study may bring out common factors in some of these cases, which so far have escaped recognition.

It will be our purpose in the second part of our presentation to discuss some of the common clinical factors observed in these two conditions. Thus it can be shown, in many instances, that both of these conditions occur in similar distinct types of individuals, and therefore a further correlated relationship would prove of particular interest. Furthermore, this subject seems to bear investigation, since there is well grounded evidence of basic similarities in the clinical background of both conditions. In order to follow this relationship, a correlation of each factor might be highly informative.

The etiologic factors must be considered since both peptic ulcer and coronary disease are affected by similar excitants. Thus Hochrein and Schleicher have emphasized the association of peptic ulcer and angina pectoris, both of which are brought on by an altered tonus of the vegetative nervous system, particularly vagotonia. Levy and Boas also suggest that the common denominator of the syndromes of angina pectoris and peptic ulcer is heightened excitability of the vagus nerve. Clinical symptoms in both conditions may be brought on by unusual physical exertion and strain, overindulgence in sports, overeating, sexual excesses, emotional upsets, etc.

The following similarity of factors is noted occurring in peptic ulcer and coronary disease: (1) both occur in nervous unstable individuals, (2) both have three basic phenomena, namely, hypersensitivity, hyperirritability and hyperactivity; (3) both occur predominantly in the non-phlegmatic individual, (4) both occur more commonly among the more intelligent and educated people, (5) both have periods of intermittency and periodicity of symptoms, (6) a similarity of personality changes occurs in both conditions, (7) both seem to have a latent period. The latency period must be considered an important factor, since both conditions may be present for long periods of time, without the patient being aware of it. (8) Although the two conditions generally originate at different age periods, this may be due to blood vessel changes and to the susceptibility with respect to time of certain structures, (9) the aggravating effects in both are not too dissimilar, (10) both occur predominantly in males, (11) The factor of race may not seem to be too important but one must give this factor consideration because both peptic ulcer and coronary occlusion occur more frequently among the white race, (12) We believe there is a pre-coronary state, similar to a pre-ulcer state, and

that the factors heretofore enumerated, if carefully evaluated, will determine it. (13) Psychosomatic phenomena as etiologic factors in the causation of peptic ulcer and coronary disease have not been totally evaluated. There appears to be a remarkable similarity of psychosomatic features which are conspicuous enough to lead to a correlation of the two diseases on a clinical basis. (14) both groups live beyond their normal tempo and capacity. Both conditions are commonly observed among high-strung individuals, and interestingly enough, these patients are often of the type who live and work under considerable stress and tension; many of them of the so-called executive type. Both conditions are more common among executive and white collar workers than laborers. (15) If there is a pre-coronary state, it should be possible to formulate a program with the object in view to remove as far as possible the tense background which is frequently associated with coronary disease. (16) In the peptic ulcer background as pointed out by us in a previous communication, there is a factor, probably endocrinologic and nervous system in origin, of a transition from adolescence to manhood, whereas in the coronary case there is the transition from middle age to pre-senility. In other words, there may possibly be a difference in age of the similarly acting organic change, vascular in origin, endocrinologically and neurogenically initiated.

SUMMARY

In 1,522 consecutive autopsies of all ages, the incidence of peptic ulcer was 6.6 per cent. This incidence

is somewhat higher statistically than generally found in consecutive autopsy studies of all ages. The incidence of peptic ulcer associated with coronary occlusion in the same series of autopsies was 10.5 per cent. The difference of 3.9 per cent in the incidence of peptic ulcer in our general autopsy data and that found among cases of coronary occlusion may not be of statistical significance. However, there were many significant similarities when the factors associated with peptic ulcer and coronary disease are considered. These factors are briefly discussed and emphasized.

It was not the purpose of this study to undertake a psychoanalytic comparison of coronary occlusion and peptic ulcer personality types, but rather to record the practical clinical observations in the anatomic and psychosomatic domains as seen by the clinician. On this basis, there evolve not only statistical data but psychosomatic data which can ultimately be applied to an understanding of the etiology of both conditions and perhaps as well to their prevention at least in part.

REFERENCES

1. Boas, E. P.: Discussion, *Am. Heart J.*, 21:689, 1941.
2. Hochrein, M., and Schleicher, I.: *Munchen med. Wchnschr.*, 88: 328, 1941.
3. Levy, H. and Boas, E. P.: *Arch. Int. Med.*, 7:301, 1943.
4. Morrison, S. and Feldman, M.: *Jour Amer. Med. Assn.*, 120:738, 1942.
5. Walsh, B. J., Bland, E. F., Taquini, A. C., and White, P.: *Am. Heart J.*, 21:689, 1941.

IMMEDIATE AMBULATION

ALFRED J. CANTOR, M. D., Flushing, N. Y.

INTRODUCTION

IN A DISCUSSION of ambulation in proctology we should distinguish between *immediate* ambulation and *early* ambulation. Early ambulation was reported as early as 1899 by Emil Ries (15) of Chicago. He allowed patients to walk about on the first to third day after vaginal celiotomies. In 1907 Boldt (1,2) described fifty cases in which ambulation was established within twenty-four hours. The majority of these patients were ambulant by the first post-operative day. A lower mortality and decreased frequency of nausea and vomiting (with less abdominal distention), were reported by this author. Boldt (1,2) also spoke of a decreased tendency toward bronchial and other pulmonary complications and circulatory disturbances. Indeed, his patients all recovered more rapidly than non-ambulatory cases of a similar type.

In 1908, however, Buedinger (3) ventured his impression that the method failed to protect against fatal embolism. That same year, in contrast, Cohn (5) and Kümmell (11) spoke optimistically of early ambulation and reported increased rapidity of wound healing.

Subsequent reports by many other authors were uniformly favorable toward early ambulation after surgery.

To bring the literature within the period of the past ten years, Vincent (17) recommended early rising,

particularly for elderly patients, on the third or fourth day post-operatively. Salishchev and Ayziks (16) advised ambulation within twenty-four to forty-eight hours after surgery, and noted a marked reduction in pulmonary complications in their cases.

Also writing in 1936 Ricci (14) advocated ambulation as early as possible after surgery. He reported immediate rising in a series of one hundred eighty patients. In the same year Flörcken (8) reported on surgery for hernias and laparotomies. In his series of eighty patients were allowed up on the first day. Correa (6) also reported in 1936, with seventy-five patients being allowed immediate ambulation. Further advocates of immediate ambulation appeared in 1937 (Gautier (9) and Cvitanovitch (7)). Additional reports appeared through 1936 and subsequent years advocating early or immediate ambulation after surgery.

In 1946, with the publication of Ambulatory Proctology (4), the role of *immediate* ambulation in proctologic procedures was stressed. The interest in immediate ambulation following proctologic surgery has grown rapidly in this country, and to some extent abroad. The usual skepticism and timidity toward any deviation from classical procedure may impede and slow further development. However, the trend is overwhelmingly favorable.

The present shortage of hospital beds will probably prove a potent factor in determining the status of early

AMER. JOUR. DIG. DIS.

and immediate ambulation after surgery. Necessity will undoubtedly lead to extensive trial, and the many advantages of early and immediate ambulation will become generally evident.

The fundamental rationale of early ambulation, and of immediate ambulation in proctology, is well established. Expert surgical technique, careful attention to hemostasis, newer hemostatic agents, the availability of antibiotics, and newer findings in physiology, will contribute to the understanding and development of early and immediate ambulation. Of particular merit in the facilitation of immediate ambulation has been the development of caudal analgesia. The use of a single puncture technique has simplified this procedure. Caudal analgesia provides excellent relaxation and exposure for surgery, and has made possible the performance of extensive proctologic surgery as office procedures.

PHYSIOLOGY

Prolonged bed rest after surgery alters physiology. If these deviations from the normal are allowed to persist serious pathologic tissue changes may develop. The extent of disruption of the general physiology is determined by the age of the patient, the nature of the surgery, the skill of the operator, the type of anesthesia, and the basic state of the patient's physiology at the time of operation.

Post-operative complications such as hypostatic pneumonia, atelectasis, venous thrombosis, embolism, intestinal distention and various metabolic disturbances, may result from disturbed physiology (remote from the area of surgery).

The function of the respiratory system, circulatory system, gastrointestinal tract, the genito-urinary tract and the nervous system—is temporarily disturbed as a consequence of prolonged bed-rest, the surgical trauma and the anesthetic. Inactivity may lead to general muscular debility.

On the other hand, if pain is eliminated and the patient is permitted resumption of normal activity as rapidly as possible, disturbances of physiology are minimal. Complications are avoided. Wounds heal more promptly. Psychologic shock is obviated.

The proctologic patient who is operated in the hospital is given an enema the night before surgery. Sedatives are prescribed, but the patient usually passes a restless pre-operative night. Other patients may be moved in or out of the same room, and nursing care—due to the present shortage of nurses—may be inadequate.

The patient is shaved either the night before surgery or the morning of operation. He receives no breakfast, and may be given another enema before operation. One or more injections of a narcotic or narcotic derivative are provided. The patient is thus weakened, tired, frightened. He is then placed on a stretcher, wrapped in a sheet and wheeled through long hallways, often into an elevator. In hallways and elevator he meets with curious stares of strangers. He is exposed to changing temperatures.

Finally he reaches the operating room where he is asked to move to the operating table. The operating room is peopled by strange creatures in white, their faces concealed by masks and caps, their attitude entirely impersonal and cold. The room itself carries the odor

of medications, recent surgery and anesthetics. Usually a spinal anesthetic is employed, and the patient is thus placed in an abnormal position upon the table for the administration of the anesthetic agent.

The patient is now placed in another uncomfortable position, often into lithotomy, for surgery. His eyes may be blinded by the strong over-head lights, and a towel may be draped over his head. A further sense of insecurity results from the feeling of being blind-folded (as if for execution).

After surgery the patient is tossed back upon the stretcher and once again goes through corridors and elevators, through changing temperatures and morbid stares, to his own room. There he remains,—the forgotten man.

The bed may be cold or too warm. The patient is apt to be covered with an excessive number of blankets, and the room is usually over-heated.

As a consequence of analgesic drugs, narcotics, et cetera, activity of the patient is suppressed.

It must be remembered that complications which develop post-operatively as a consequence of surgery and confinement to bed are often indirect and remote. They are a result of reactions mediated through the autonomic nervous system, through the respiratory, the circulatory, the genito-urinary and the gastro-intestinal systems. It would perhaps be more correct to say that the abnormal physiology results from impulses passing through both the cerebro-spinal and the autonomic nervous systems. Reflex reactions occur at both conscious and unconscious levels. The entire body structure is involved in these reactions.

Our primary concern here, however, is with the reflex reactions involving the zones of complications, the respiratory system, the vaso-motor system, the genito-urinary system and the intestinal tract.

The physiologic changes involving the pulmonary system, the diaphragm and the muscles of respiration, include diminished vital capacity and tidal air as a consequence of limited respiratory excursion, resultant hypoventilation and the accumulation of bronchial secretion. Mucus plugs form in the bronchi, resulting in atelectasis. The reduced respiratory excursion, reduced vital capacity and tidal volume of air, is most marked after abdominal surgery. We will not here describe the effects of various types and locations of abdominal incisions.

There is need to discuss, however, the effect of prolonged bed rest on respiration. The work of Haldane, Meakins and Priestly (10) has demonstrated that pulmonary ventilation is inadequate in the recumbent position. A slight anoxemia develops. If the patient has cardiac insufficiency the effect on pulmonary ventilation will be even more pronounced. If the patient must be recumbent deep breathing is essential to prevent anoxemia.

Frequently the patient will voluntarily inhibit cough either as a consequence of pain, or to avoid tearing stitches in the rectal area. The danger of bronchial obstruction by mucus is thus further increased.

Reflex reactions within the gastro-intestinal tract may resolve in hypotonicity and hypomotility. Intestinal distention may develop. Nausea and vomiting may result in dehydration. Intestinal distention further limits respiratory excursion of the diaphragm.

Pressure on the large abdominal veins may impair venous circulation within the legs, resulting in an increased tendency toward thrombus formation.

These reactions of the intestinal tract may result entirely from emotional disturbances attendant upon surgery. The action of the emotions upon the autonomic nervous system is well known. The colon has long been designated as the "sounding board of the emotions." We cannot overly stress the importance of psychologic factors in the control of surgical problems.

Wherever possible normal bowel function should be initiated shortly after surgery. Enemas should not be employed unless indicated.

Reflex disturbances within the circulatory system result in stagnation and pooling of blood. This may be followed by thrombosis, thrombophlebitis, embolism and infarction.

In any surgical procedure there is a certain amount of local loss of fluid. Blood loss should be kept minimal by minute and prompt attention to surgical hemostasis. In proctologic surgery the blood loss is usually of little consequence, unless we are dealing with extensive colon resection. Reflex reactions within the vasomotor system may result from pain and fear.

Stagnation of blood, especially in the lower extremities and viscera, results in reduced circulatory efficiency, decreased effective blood volume, and impaired tissue metabolism. Functional disturbances throughout the body must inevitably follow. Surgical shock may thus develop.

This is a complex situation involving capillary permeability, blood volume, the efficient removal of waste products from the blood stream, vascular tone, changes within the blood itself—oxygen content, effect on the clotting mechanism, concentration, viscosity, et cetera,—and functional disturbances in remote areas, involving the pulmonary tree and renal function. Vascular reactions are closely related to respiratory function and the degree of anoxemia.

They are also closely related to emotional factors, and complete circulatory collapse may be a consequence of very minimal surgery if the patient is sufficiently disturbed emotionally. It must be stressed that the effect on the circulatory system is not entirely dependent upon extended surgery. Psychogenic factors are of extreme importance.

We must also mention the mechanical factors resulting from lying in bed. There is pressure on the legs, decreased respiratory activity, generally decreased muscle tone, and possibly increased intestinal distention with reduced return venous flow from the lower extremities.

The poor muscle tone and diminished circulation may result in lesions of the intima of the vessels and thrombus formation. Pulmonary embolism may follow.

IMMEDIATE AMBULATION AND OTHER IMPORTANT POST-OPERATIVE FACTORS

The value of immediate ambulation now becomes evident. The above described disturbances of physiology can be prevented by immediate ambulation. However, this one factor alone is not sufficient. It is essential that emotional disturbances be minimized before, during and after surgery. Careful attention must be given to the prevention of dehydration and the maintenance of adequate nutrition.

The psychological factors will bear further discussion. When a patient presents himself with a surgical proc-

ed condition surgery should not be postponed. The waiting period between the time of diagnosis and the time of availability of a hospital bed offers an opportunity for the development of serious emotional reactions. During that waiting period the patient imagines most direful consequences. He envisions a fearsome operating room, horrible and grotesque operating instruments and final death, either on the operating table or shortly thereafter. Many patients still believe that the hospital is "the place to go to die." Sleep is disturbed or does not come at all. The fear and horror that result produce psychologic shock even before the patient reaches the operating room. Thus, if surgery is indicated it should be performed as rapidly as possible, once the diagnosis is made.

If the patient can be operated at once, in the office, no delay should be permitted. The surgeon does the patient no service by permitting an interval of even a single day between the time of diagnosis and the time of surgery.

Whenever it is possible to avoid hospitalization the patient should be given the benefit of immediate office surgery. If hospitalization is essential the patient should be operated the same day or the next day. Of course this does not apply to those cases requiring extensive preparation of the colon for major resection.

Nurses and attendants should be instructed to act with solicitude and care. The impersonal hospital and operating room atmosphere should be dispelled. A restful green color might be employed in hospitals generally and in operating rooms particularly, to replace the dead, stark white usually seen. A radio should be routine equipment in every patient's room. Indeed, I believe that it should be in every operating room. A record player could be employed if desired, with a selection of music to suit the individual patient's taste.

The surgeon should be friendly throughout the operation, when the patient is awake, and should engage the patient in casual conversation unrelated to his condition. If the surgeon does not wish to talk during surgery a nurse or an attendant at the head of the table may assume this function. In other words, every effort must be made to keep the patient at ease and to avoid the usual drama of an operating room.

Little need be said about surgical technique. We need merely emphasize the need for careful hemostasis and minimal trauma to tissues. A minimum amount of packing should be inserted into the rectum, and this should be removed within twenty-four hours.

Adequate nutrition must be maintained, and my patients are permitted all foods with the exception of fruits, fruit juices and raw vegetables, immediately after surgery. Parenteral fluids are rarely necessary but may be useful in those cases that evidence dehydration as a result of vomiting. The maintenance of electrolyte and fluid balance is very simple in the ambulatory patient. Immediate ambulation improves the circulation of all body fluids. My patients are all allowed a full diet twenty-four hours after surgery.

The prevention of post-operative pulmonary complications requires minimal surgical trauma and the control of post-operative pain, immediate ambulation, and an upright position for coughing, if necessary. The improved circulation resulting from an erect position and walking is very important.

The avoidance of confinement to bed, immediate

walking, and a healthy emotional attitude, will prevent secondary complications. These factors, and a rapid return to normal bowel function, will prevent gastrointestinal complications. One ounce of mineral oil is prescribed for the night of operation and is continued nightly thereafter until normal bowel function is established. A full, adequate diet, within twenty-four hours post-operatively, is another important factor in re-establishing normal bowel activity. If there is no bowel movement within forty-eight hours after surgery a rectal mineral oil instillation for retention may be indicated. Enemas are not often necessary.

There are other factors of great importance in the post-operative management of these patients. The judicious use of antibiotics where required must be mentioned. Sitz baths, general cleanliness, the use of healing ointments, local attention to the quality and grade of healing, digital manipulation where indicated,—all are important contributory factors toward adequate wound healing. There seems little doubt that immediate ambulation increases the rate and improves the quality of wound healing. However, these patients must all be observed for a period of one to three months post-operatively to avoid the development of post-operative stenosis or stricture.

CONCLUSIONS

The history of early ambulation is described, the earliest known report being in 1899. Early ambulation is distinguished from immediate ambulation. Immediate ambulation in proctologic procedures has been stressed since 1946 (with the publication of Ambulatory Proctology (4)). The interest in immediate ambulation after proctologic surgery has increased tremendously, and the results are overwhelmingly favorable.

The present shortage of hospital beds, the increasing economic dislocation (negative factors), improved quality and rate of healing, the absence of post-operative complications and elimination of hospital costs (positive factors), have favored the development of immediate ambulation.

The altered physiology resulting from prolonged bed-rest is described. Complications such as hypostatic pneumonia, atelectasis, venous thrombosis, embolism and thrombophlebitis, intestinal distention and other

metabolic disturbances, are all avoided by immediate ambulation. The psychologic shock of hospitalization, the usual operating room management and the usual bed-rest, are all avoided by the technique of immediate ambulation.

It is clearly evident that immediate ambulation is the procedure of choice in proctologic surgery.

REFERENCES

1. Boldt, H. J.: The management of laparotomy patients and their modified after treatment. New York M. J., 85:145-153, (January 26) 1907.
2. Idem: How long must patients observe absolute rest in bed after abdominal operations? Tr. Am. Gynec. Soc. 32:181-185, 1907.
3. Buedinger, K.: Ueber das Aufstehen nach chirurgischen Operationen. Wien. klin. Wchnschr. 21:1694, 1908.
4. Cantor, Alfred J.: Ambulatory proctology. New York, Paul B. Hoeber, Inc., 1946.
5. Cohn, F.: Das Frühaufstehen der Laparotomierten. Zentrabl. f. Gynäk., 32:1233-1237, 1908.
6. Correa, B.: Immediate or early rising: 138 cases. Rev. brasil. de med. e farm. 12:3-11, 1936; Lyon chir. 34:37-48 (January-February) 1937.
7. Cvitanovitch: Le lever immédiat des opérés. Presse méd. 45: 1471, 1937.
8. Flörcken, H.: Über das Aufstehen nach chirurgischen Operationen. München. med. Wchnschr. 83:917-919, (June 5) 1936.
9. Gautier, J.: La chirurgie sous les rayons infra-rouges et ultra-violetes. Gaz. méd. de France, 44:791-794, 1937.
10. Haldane, J. S., Meakins, J. C. and Priestley, J. G.: The effects of shallow breathing. J. Physiol. 52:433-453 (May 20) 1919.
11. Kümmel, H.: Abkürzung des Heilungsverlaufs Laparotomierter durch frühzeitiges Aufstehen. Arch. f. klin. Chir. 86:494-508, 1908.
12. Idem: Weitere Erfahrungen über frühzeitiges Aufstehen Laparotomierten zur Sicherung und Abkürzung des Heilverfahrens. Deutsche med. Wchnschr. 35:1865-1869, 1909.
13. Leithausen, Daniel J.: Early ambulation and related procedures in surgical management. Springfield, Illinois, Charles C. Thomas Publisher, 1946.
14. Ricci, G.: Sobre el levantamiento inmediato de los operados. An. de cir. 2:175-207 (August) 1936.
15. Ries, Emil: Some radical changes in after treatment of celiotomy cases. J. A. M. A., 33:454-456, August 19) 1899.
16. Salishev, V. E. and Aysika, I. G.: Active postoperative regimen (early rising). Novy khir. arkhiv. 36:260-277, 1936.
17. Vincent, G.: Le Lever précoce en chirurgie abdominale. J. de méd. de Paris, 56:252-253 (September 24) 1936.

SUCCESSFUL OINTMENT THERAPY FOR PRURITUS ANI

LAURENCE G. BODKIN, M. D.,* AND EDGAR A. FERGUSON, JR., (CHEMIST), Brooklyn, N. Y.

PRURITUS ANI HAS always been difficult to treat and a problem of real importance to the patient and physician. The disease occurs in apparently healthy individuals and is characterized by a marked history of itching of the perianal skin which becomes reddened, fissured, and sometimes moist and macerated.

Numerous shallow fissures are usually present, often extending back to the coccyx and often anteriorly to the scrotum or vagina. The presence of whitish edges of skin along these fissures and even beyond is often observed. External hemorrhoids or tags are usually

thickened and when excised (which is rarely done) the wounds heal sluggishly with the same white, fibrotic edges.

Many causes have been advanced for pruritus ani. By reason of the symptomatic relief produced the nervous system has been the target of attack both by means of local anesthetic agents and by means of antispasmodics and sedative agents. There is a long list of so-called causative agents such as: fistulae, infected crypts, fissures, food allergy, hepatic insufficiency, caustic soap, pin worms, and others.

These, together with the nervous syndrome, comprise the group which may be medicated collaterally with good results.

Submitted June 2, 1950.

*Diplomate, American Board of Proctology.

FEBRUARY, 1951

The remainder comprises a great bulk of cases which must be treated directly and the long list of treatments suggest that no single good result has been obtained. This large group may be called "essential" pruritus and no satisfactory treatment has yet been discovered.

Attempts at imitating the action of pruritus on healthy skin led to the use of an agent known as ammonium oleate. This causes actual pruritus in some cases. In addition, experimental evidence has shown that the irritant forming the whitish edges of skin along the fissures may be reproduced at the same time by an astringent agent such as tannic acid. Another series of compounds inducing irritation similar to pruritus ani is the ammonia series. Dilute solution of ammonia water reproduces many of the itch symptoms. Finally, the general condition of poor nutrition in the area of pruritus ani may be reproduced by an ointment containing large amounts of microscopic crystalline methionine (an amino acid).

To sum up the experimental clinical findings in reference to causative agents we have the following list:

- (1) ammonium oleate
- (2) tannic acid
- (3) ammonia water
- (4) microscopic crystals of methionine

Astringent, direct irritant, or protein precipitate properties reproduce pruritus ani in healthy skin. Together with the specific finding in reference to methionine this knowledge will aid considerably in elaborating the mechanism causing this treacherous disease. It is entirely possible that a combination of the excretion leaking from the anus and the excessive amount of sweat found in the perineal area combine to cause pruritus ani, whenever the nutrition of the skin is so changed to allow the result.

In vitro, the above irritants are best counteracted by buffered protein or buffered amino acid solution. For this reason various forms of protein and amino acid solutions were applied with considerable success. The final development consists of an amino acid mixture derived from lactalbumin from which is removed the more readily water-insoluble amino acids such as methionine. This combination is incorporated in a saturated fatty acid di-ester of polyethylene glycol* base yielding a stable ointment. When applied to the affected areas immediate relief is obtained, and, within a week there is complete alleviation of pruritus symptoms.

The skin changes which take place while healing are easily observable and are both interesting and significant. The moisture disappears first. This is followed by fading of redness in inflamed areas. The white ridges where precipitation of protein has been pronounced become less noticeable, until finally the perianal region assumes its normal color. The change in texture is even more marked. The fibrotic, inelastic skin which fissures readily becomes soft and pliable. Within a few weeks' time there is every appearance of normal skin.

*Carbowax (a registered trade-mark).

Separate applications were made of the amino acids listed in the table below:

AMINO ACID	EFFECT
Arginine	Indifferent
Histidine	Slight irritation
Lysine	Indifferent
Tyrosine	Indifferent
Tryptophane	Slightly beneficial
Phenylalanine	Slightly beneficial
Cystine	Slightly irritating
Methionine	Strongly irritating
Threonine	Indifferent
Leucine	Slightly beneficial
Isoleucine	Indifferent
Valine	Slightly beneficial

Methionine was definitely irritating, others were indifferent or of some benefit. It is the mixture of amino acids from which methionine has been largely removed which gives the best and most lasting results.

Salve was applied in every case to the perineal area and if necessary around the vaginal or scrotal areas as well. Most patients reported immediate cooling effect from the salve. This effect lasted for approximately 24 hours. In rating patients the severity of the original difficulty is noted as 1, 2, or 3. One represents itching during the day only with little interference with work. Two represents itching both day and night with some interference with sleep. Three represents day and night itching with extension to vagina or scrotum which causes interference with both work and sleep.

In the group tested there were 100 cases. The average severity as noted in protocol is 2.5. Relief was experienced immediately in 98 cases. The time is noted for complete clearing of symptoms in protocol. The average time is 19.5 days. In the group there were 10 cases which had only partial relief and 2 cases with no relief. This represents a percentage of 88% complete success.

CONCLUSIONS

This mixture of amino acids is a specially treated combination from which excess methionine has been removed. This mixture incorporated in a base of a saturated fatty acid di-ester of polyethylene glycol makes a salve, which when applied to areas of pruritus, has shown a superiority far better than anything expected in the treatment of pruritus ani.

BIBLIOGRAPHY

- Herrin, R. C.: Secretion of Ammonia by Small Intestine of Dog, *Amer. Jour. Physiol.*, 1940, 129-146.
- Williams, J. L. and Dick, G. F.: Excretion of Non-Protein Nitrogen Substance by the Intestine, *J. A. M. A.*, 1930, 100-484.
- Benedict, S. R.: Uric Acid in its Relation to Metabolism, *Harvey Lectures*, 1915-1916, 11-346.
- Bodkin, L. G.: Oral Therapy for Pruritus Ani, *Amer. Jour. Digest. Dis.*, Vol. 12, No. 8, Aug. 1945, 255-257.
- Bodkin, L. G.: Pruritus Ani: A Review of Oral Therapy, *Amer. J. Digest. Dis.*, Vol. 14, No. 3, Mar. 1947, 109-113.
- Bodkin, L. G.: Pruritus Ani, *Amer. Practitioner*, Vol. 2, No. 9, May 1948, 580-581.

CHRONIC PEPTIC DUODENAL ULCER WITH CANCEROUS TRANSFORMATION

E. F. GEEVER, M. D., V. L. BOLTON, M. D., AND N. W. FAWCETT, M. D., Colorado Springs, Colorado.

THE INCIDENCE OF malignant change in peptic ulcers of the duodenum is exceedingly low as compared with neoplastic changes in gastric ulcers. Ewing (1) found only ten cases in a review up to 1940. This is true also of primary cancers of the first part of the

patient complained of pain in the mid-epigastrium, particularly after a heavy meal, and associated with distention and bloating. The pain was made worse by rich or fried foods or by roughage. The pain was usually associated with much rumbling and gurgling in the abdomen, presumably from excessive amounts of gas. There had been a 14 pound weight loss during the previous three months. There was no history of vomiting and the history was negative also for blood in the stools and jaundice. The patient had had a normal menopause many years previously and had had no vaginal discharge or bleeding since. Additional complaints on admission included burning and frequency of urination with some pain in the left flank which radiated toward the genital region. Physical examination on entry revealed an elderly white female lying quietly in bed and not acutely ill. The head and neck examinations were negative. The chest was clear to percussion and auscultation and the heart sounds were normal. The abdomen was soft but slightly distended. There was some tenderness in the epigastrium in the midline and also some tenderness over the left kidney. No abdominal masses could be felt. There was slight defensive rigidity in the epigastrium but not in the lower abdomen. Auscultation of the abdomen revealed hyperactive peristalsis. Rectal examination was negative except for hemorrhoids. Laboratory studies showed: urinalysis—S. G. 1.012; chemical examination was not remarkable; 3 to 4 pus cells and 2 epithelial cells per high powered field; blood—RBC 4,879,000, WBC 5,300 with a normal differential; blood chemistry NPN 49 mgm. %. X-ray studies revealed: the gall bladder following ingestion of dye showed poor concentration and a large, non-opaque stone was visible. Roentgen examination of the gastro-intestinal tract following a barium meal revealed a greatly dilated stomach with 100% retention of barium at the end of two hours; the duodenal cap was deformed and showed evidence of an ulcer crater (See Figures I and II). Examination of the remainder of the intestinal tract



Fig. 1.—Roentgenogram of stomach and duodenum. An oblique view of the stomach and duodenal bulb showing the elongated enlarged stomach with a well defined pyloric canal and markedly deformed duodenal bulb with the crater.

duodenum independent of peptic ulceration in contrast to the incidence of tumors in the second portion. The purpose of this report is to present another case of cancerous change in a chronic peptic duodenal ulcer. The cancer was unsuspected even on gross pathologic examination and microscopic study revealed the true nature of the lesion.

CASE REPORT

This 74 year old white female entered St. Francis Hospital for the first time on September 2, 1949. Her history dated back four years when a diagnosis of peptic ulcer and gall-bladder disease was made at an out-of-state hospital. She was placed on dietary management at that time with prompt improvement. Improvement was sustained until April, 1949, when her digestive symptoms recurred. The symptoms increased in severity up to the time of admission. On entry the

From the Departments of Pathology, Radiology and Surgery of St. Francis Hospital, Colorado Springs, Colorado.

Submitted May 9, 1950.

FEBRUARY, 1951



Fig. 2.—A lateral view of the stomach and duodenal bulb again depicting the deformity of the bulb and revealing its distance from the pylorus and antrum.

showed several barium-filled diverticula in the region of the sigmoid; intravenous pyelogram was normal. The clinical impression was duodenal ulcer, cholelithiasis and sigmoid diverticulitis. The patient improved on dietary management and bed rest and was discharged on September 8, 1949. She was readmitted, however, on September 13, 1949, with a history of pain and vomiting of coffee-ground colored material. Laboratory studies at this time showed: blood—RBC 4,830,000, WBC 7,800 with a normal differential. The patient was treated with bed rest, diet, heat to the abdomen and analgesics. She improved again and was discharged on September 22, 1949. She was admitted for the last time on January 13, 1950, complaining of epigastric pain and vomiting of bile-stained material. The pain at this time radiated to the back. Physical examination revealed findings similar to those on previous admissions except for marked tenderness and rigidity of the entire upper abdomen. Urine and blood examinations at this time were non-contributory; gastric analysis showed a fasting hydrochloric acid level of 33 units. Blood was present in the gastric specimen; blood chemistry—total plasma proteins 5.52 grams %. The patient did not make any improvement on medical management. Therefore, operation was performed on February 3, 1950, and a large obstructing ulcer was found on the anterior wall of the first part of the duodenum. The stomach was large and thin-walled. The gallbladder was also enlarged, thickened and contained a large stone. Bilateral vagotomy, anterior gastro-jejunostomy and cholecystostomy were performed. The immediate post-operative course was uneventful. Continuous gastric suction was maintained for four days and intermittently thereafter. Urecholine was given in usual dosage. Acid-base balance was satisfactorily maintained. However, the stomach was not yet emptying on February 12, 1950, and while her general condition was satisfactory, parenteral nutrition was becoming a serious problem and it was believed advisable to perform jejunostomy for further feeding. This was done on February 12, 1950. At exploration the gastro-jejunal stoma was found intact, but because of some dilatation of the proximal jejunal loop, jejunostomy was performed as well as a jejunostomy. The patient tolerated this procedure well and her general condition was satisfactory for eighteen hours at which time she died very suddenly.

At autopsy a large duodenal ulcer, 3.5x3.0 cms. in surface area, was found immediately post-pyloric in position. One margin abutted on the pylorus. The margins were reddish-yellow, prominent, raised and firm. The base was deep, fibrous and ivory colored. Gastro-enterostomy, jejunostomy and cholecystostomy sites appeared intact. The heart was dilated, globular in shape and weighed 470 grams. The lungs showed acute passive congestion and pulmonary edema. Microscopically, the ulcer base revealed infiltration by anaplastic epithelial cells in regular glandular patterns, columns or nests. The cells ramified deeply into the muscle and serosal layers. They presented pale basophilic oval, indented or polyhedral nuclei and moderately abundant basophilic cytoplasm. Some nuclei were hyperchromatic. Mitotic figures were scattered throughout. (Figures III and IV) There were no metastases. Death had resulted from acute cardiac failure.

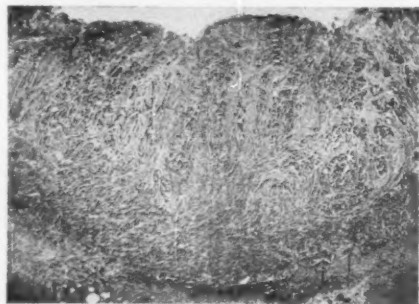


Fig. 3.—Duodenal ulcer base (magnific. 15x). Section shows deep infiltration by anaplastic epithelial cells in irregular glandular patterns, columns or nests.

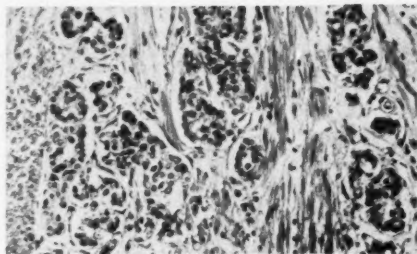


Fig. 4.—Duodenal ulcer base (magnific. 200x). Anaplastic cells are apparent in nests or small glandular patterns.

COMMENT

Several features of this presentation warrant discussion. In the first place, it seems essential to rule out cancer of the pylorus, gall bladder or pancreas growing into the first part of the duodenum. Histologic examination of multiple planes of the duodenal ulcer showed the major amount of cancerous tissue in the ulcer base with tapering off into adjacent tissue. Multiple sections of the pancreas and gall bladder showed no evidence of cancer. The diagnosis of obstructing duodenal ulcer was made by X-ray approximately five months before death and verified by several surgical explorations and at necropsy. The lesion, at necropsy, abutted on the pylorus, as is so often the case with duodenal peptic ulcer, but was unquestionably post-pyloric in position. The complicating cholecystitis and cholelithiasis renders interpretation of digestive symptoms difficult. The patient had a history of digestive upsets going back four years, but whether due to duodenal ulcerative changes or cholecystitis or both is difficult to assess. The difficulty of obtaining an adequate history in aged patients with chronic peptic ulcer was stressed by one of us in a previous study (2).

The next question is whether this was ulcerative carcinoma to begin with or cancerous change in a chronic peptic ulcer. Stewart (3) mentions histologic criteria of value: ulcerative carcinoma causes little or no destruction of the wall and obliterative vascular changes are absent. Chronic peptic ulcer, on the other hand, is always accompanied by fibrous changes and often with obliterative vascular changes. In this instance considerable fibrosis was found in the ulcer base. (Figure III).

The large size of the ulcer, 3.5x3.0 cms. in surface area, is suggestive of a cancerous lesion. In peptic ulcers of the stomach this point is often stressed. Feldman (4) points out that large sized duodenal ulcers are rare, but that when they do occur they become malignant. A large sized ulcer associated with this degree of roentgenologic deformity and progressively becoming worse in appearance despite clinical quiescence should raise some doubt as to secondary carcinoma. However, cancerous transformation is so rare in duodenal ulcers that surgery is more likely to be performed with the pre-operative diagnosis of intractable ulcer rather than with the hope of curing an ulcer which became cancerous. As noted above it was our clinical opinion that this was an old duodenal ulcer with scar contraction. Grossly at autopsy it had the same appearance. Routine

photography of interesting surgical and necropsy pathologic specimens is performed in this hospital. However, this case was not photographed because the lesion grossly was considered commonplace and there were already many examples of chronic duodenal ulcers in our photographic files. Cancer was not suspected until the microscopic examination. For the most part we feel this diagnosis will be made by the Pathologist rather than the Roentgenologist. In a presentation of two cases of ulcerative carcinoma of the first part of the duodenum, Kleinerman, Yardumian and Tamaki (5) stressed the roentgenologic appearance and erroneous diagnosis of diverticula. Such a roentgenologic appearance was not present in our case. In this patient we are dealing with cancer occurring secondary to a chronic duodenal ulcer and at this early stage of malignant transformation the lesion could not be expected to present roentgenologic signs other than those of a non-healing duodenal ulcer.

SUMMARY

1. A case is reported of chronic peptic ulcer of the first part of the duodenum with cancerous change in a 74 year old white female.

2. There were no metastases and microscopic examination of the lesion revealed its true character.

REFERENCES

1. Ewing, J.: *Neoplastic Diseases*, W. B. Saunders, 4th Edition, 1940, Phila. p. 721.
2. Geever, E. F.: *Fatal chronic peptic ulcer in the aged*, Rocky Mountain Medical Journal, 46:553-558, 1949.
3. Stewart, M. J.: *Pathology: general relation of cancer to ulcer*, British Medical Journal, 2:882-886, 1925.
4. Feldman, M.: *Clinical Roentgenology of the Digestive Tract*, Williams and Wilkins, 1945, Baltimore.
5. Kleinerman, J., Yardumian, K. and Tamaki, H. T.: *Primary Cancer of the Duodenum*, *Annals of Internal Medicine*, 32:451-465, 1950.

A CASE OF ACUTE CHOLANGITIS (POST-OPERATIVE) DUE TO PROTEUS VULGARIS SEPSIS TREATED WITH AUREOMYCIN

A. ALLEN GOLDBLOOM, M. D. F. A. C. P. AND MAURICE GOLBEY, M. D., New York, N. Y.

WITH THE RAPID advance of chemo-therapy in the fight against infectious diseases, it is considered worthwhile to report a case of acute cholangitis (lenta) with blood and bile cultures showing *Proteus Vulgaris* cured by the new antibiotic aureomycin.

CASE REPORT

History: R. D., a 56 year old white male, was admitted to Metropolitan Hospital on October 6th, 1949 because of chills, fever and epigastric pain of twelve hours duration.

Past history revealed that nine months previously there was an operation of cholecystectomy because of cholecystitis, cholelithiasis and jaundice. The patient's post-operative course was uneventful. He was well until the day before admission when he complained of chills, fever and vomiting.

Physical examination: On admission physical examination revealed a well developed, well nourished white male in acute distress, dyspnea and cyanosis. The temperature was 103°; respirations 32; pulse 100; blood pressure systolic 110, diastolic 60. Jaundice was not present at this time. The skin was warm and moist. There was no nuchal rigidity nor adenopathy. The heart revealed no abnormal sounds. There was dullness to percussion over the right lobe posteriorly with diminution of the breath sounds. There was marked tenderness and spasm in the right upper quadrant region. The scar of the previous operation was well healed.

Laboratory data: Hb. 15.5 gms., RBC 5,500,000, WBC 16,500, neutrophils 82% (30% non-segmented), lymphocytes 14%, monocytes 4%. Urine: specific gravity 1.025, cloudy, amber, pH 7.5, albumin 1 plus, sugar negative, microscopic negative.

Chest x-ray revealed increased hilar markings and increased truncal markings radiating toward the periphery and bases of both lungs. Flat plate of the abdomen was negative as well as that of the stomach and duodenum.

Cultures of the blood and nasopharynx were planted and the patient was given penicillin because of the possibility of a right lower lobe pneumonia. The day after admission it was noted that the patient's sclerae were icteric and that the skin was yellow. On the third hospital day the temperature rose to 104°. The patient experienced two bouts of chills and

the jaundice deepened. Tenderness in the right upper quadrant persisted. The liver was palpated two fingers below the costal margin. These findings suggested cholangitis and the patient was placed on streptomycin.

The first blood culture was reported negative while the second revealed a growth of *Bacillus proteus*. A repeat blood culture four days later again showed *Bacillus proteus* and indicated that this organism was not a contaminant. The patient was continued on penicillin and streptomycin. Although the pain in the right upper quadrant region diminished, the enlarged liver persisted. The temperature showed little response to therapy. Blood cultures drawn on October 15th, 22nd, 25th, and 26th all revealed *Proteus Vulgaris*. Biliary drainage on October 26th showed many epithelial cells, pus cells and dense mucus strands. Culture of this drainage revealed *Bacillus proteus vulgaris*.

The failure of the penicillin and streptomycin to control the infection (as shown in the temperature curves of Fig. I) and the persistence of the *Bacillus proteus* bacteremia made us look for a more effective antibiotic for this very sick patient. On October 24th (18 days after admission) aureomycin (100 mg. four times a day) was substituted for the penicillin and streptomycin. On the third day of its use, the temperature fell to normal. Five blood cultures taken during the aureomycin therapy were all negative. The patient continued to improve rapidly.

The liver function tests (Fig. II) showed some liver damage as evidenced by the low cholesterol ester and low serum albumin. There was a gradual improvement in the liver findings, the Cephalin flocculation test finally becoming negative, the alkaline phosphatase normal, and the cholesterol-cholesterol ester percentage normal as well as the total proteins with a normal albumin-globulin ratio.

DISCUSSION

Aureomycin, one of the latest antibiotics, is a yellow crystalline powder obtained from the mold *Streptomyces Aureofaciens*, a member of a group of fungi called ultramolds (1). It has been found effective against numerous Gram positive and Gram negative organisms, as well as some rickettsial and viral infections (2,3). It is bacteriostatic rather than bactericidal in its effect (4).

It is beyond the scope of this paper to discuss the value of aureomycin in the various clinical conditions

From the Medical Service of the New York Medical College, Flower and Fifth Avenue Hospital (Metropolitan Hospital Division).

Submitted Apr. 25, 1950.

FEBRUARY, 1951

Date	Icterus Index (Units)	Van den Bergh (Reaction)	Cephalin-Cholesterol Precipitation Test	Alkaline Phosphatase (Bodansky Units)	Cholesterol mg./100 cc.)			Serum Values (gm./100 cc.)				
					Total	Ester	% of Total	Total Proteins	Albumin	Globulin	A/G Ratio	
10/10/49	78	weak immed.	pos.	+	8.5	191	46	24%	5.1	3.3	1.8	1.8 : 1
10/13/49	39	weak immed.	pos.	++	8.5	264	132	50%	4.7	2.1	2.6	0.8 : 1
10/17/49	15	immediate	pos.	++	8.2	194	118	61%	5.2	2.6	2.6	1.0 : 1
10/19/49	25	weak immed.	pos.	++	8.0	178	126	71%	4.4	2.1	2.3	0.9 : 1
10/24/49	9	weak immed.	pos.	++	8.0	176	108	61%	7.1	2.9	4.2	0.7 : 1
10/31/49	8	weak delayed	pos.	++	8.2	133	94	71%	6.1	2.2	3.9	0.57 : 1
11/ 7/49	9	negative	0	0	4.6	140	97	69%	6.9	3.3	3.6	0.9 : 1
12/21/49	5	negative	0	0	2.7	224	143	64%	7.0	4.1	2.9	1.4 : 1

Figure II—Laboratory tests showing non-obstructive liver parenchymal damage returning to normal in a case of acute cholangitis due to *Proteus Vulgaris* Sepsis.

such as atypical pneumonia, (5,6,7,8) brucellosis, (9, 10,11) rickettsial diseases, (12,13) urinary tract infections, (14,15) etc. Our purpose is to show its effect in a case of sepsis due to *Proteus Vulgaris*. Our encouraging results with the drug are in fact opposed to the findings of Long et al (15) who reported that aureomycin was of no value in *Proteus Vulgaris* infections as contrasted to its definite value in staphylococcal bacteremia (15,16,17,18).

Herrell and Heilman (19) found that aureomycin is concentrated in the liver (8 to 16 times) and excreted in the bile. Whether or not this same concentration would occur in the bile under conditions in which there is definite infection and hepatic damage could not be stated at that time. They question whether aureomycin would prove effective in the treatment of infections involving the biliary tract.

Bacteriology: The genus *Proteus* comprises a group of soil and water saprophytes, common in decaying animal or vegetable matter. They may often be found in the human intestine, or as opportunists in infections (especially cystitis) of man. They may cause disease in lower animals. *Proteus* has been occasionally implicated in outbreaks of gastro-enteritis. *Proteus Vulgaris* is a non-spore forming, gram negative, motile rod commonly found in feces, stagnant water, or any moist solid medium. The *Proteus* species may be grouped with the Enterobacteriaceae (20).

Materials submitted for its examination are usually feces, urine, and pus, which may be plated in the same manner as bacillus typhosus. Growths of *Proteus* are often mistaken for intestinal pathogens on desoxycholate agar plates. Since the medium almost entirely inhibits spreading, the colonies of *Proteus* are small, colorless, and may resemble those of *Salmonella*, *Eberthella*, and *Shigella* (21).

This patient presented one of the symptoms found in post-cholecystectomy syndrome—acute cholangitis. Other common manifestations of the syndrome are dyskinesia of the sphincter mechanism, retained cystic duct, common duct stricture or pancreatitis (22).

DIFFERENTIAL DIAGNOSIS

Right lower lobe pneumonia was considered by some of the clinicians because of the rales with compression sounds. This undoubtedly was due to atelectasis of the lungs by a high diaphragm and corroborated by negative chest x-rays. The exquisite tenderness over the

upper abdomen was suggestive of subphrenic abscess. The fluoroscopic examination excluded this condition because of the freely movable diaphragm. However one must not forget that subphrenic abscesses may be situated in other areas than between the diaphragm and liver, e. g. beneath the liver and subhepatic area. This may have had to be considered if the laboratory data had not been of significance. Perforated or penetrating peptic ulcer was excluded because of the absence of abdominal rigidity and tenderness beyond the epigastric area. X-rays of the gastrointestinal tract revealed no significant findings.

The long time interval of nine months post-operatively excluded stricture of the duct. A recurrent stone with obstruction and ascending bile duct infection could produce the presenting syndrome. It was shown after cholecystectomy the duct may be so dilated as to try to assume the function of the removed organ (23). With such dilatation of the duct, infection may be more easily produced. X-rays of the abdomen excluded a calculus in the regions of the gallbladder, ducts, and pancreas. The absence of a marked duodenal sweep and the normal appearance of the stomach and duodenum excluded an enlarged head of the pancreas or peptic ulcer.

The sudden onset of chill, temperature and jaundice suggested secondary bile duct infection or cholangitis. The fact that the duodenal drainage revealed an organism on culture similar to that found in the blood on several occasions (*bacillus Proteus Vulgaris*) is proof beyond doubt that the patient had a bacteremia or septicemia. Contamination could not be considered. Twiss and Carter found on biliary drainage before and at operation in their active cholangitis cases that *Escherichia coli* were mostly found. A few cases showed *Eberthella typhosus*, *Bacillus Welchii*, streptococcus, staphylococcus and mixed organisms (24).

A primary focus of sepsis in a hollow viscus is not rare (25). In the bile ducts, typhoid bacillus, paratyphoid, colon bacillus, pneumococcus, and streptococcus viridans are the most frequent invaders. Microbic infection of the bile and extrahepatic biliary duct system originates either from the liver, the intestine, or from the submucosal capillaries (26,27). The nature of the biliary flora is affected by the acidity of the bile and by its lack or low content of protein and carbohydrate. The most important determining factor is the state of oxidation of the bile. The lower tract of the common duct allows aerobic as well as anaerobic de-

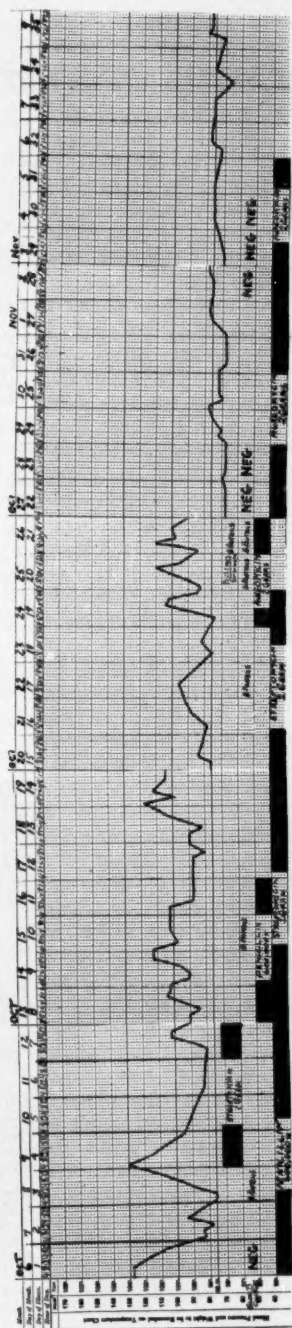


Figure 1. Temperature curve showing the effect of aureomycin in a case of acute cholangitis due to *Proteus Vulgaris* Sepsis

velopement. The gallbladder and upper portion of the duct system offer strictly anaerobic conditions. The fate of microorganisms in the bile depends on the reaction of the bile toward its invaders (28).

CONCLUSIONS

1. A case of acute cholangitis (lenta)—post-cholecystectomy syndrome—revealing *Proteus Vulgaris* on culture of blood and biliary drainage is presented.

2. Differential diagnosis excluded pneumonia, subphrenic abscess, penetrating or perforating peptic ulcer, enlarged head of the pancreas, or recurrent stone as the cause of the fever, chills, abdominal pains and jaundice.

3. This is the first reported case to date of a *Proteus Vulgaris* Sepsis treated and cured by aureomycin.

4. Since cholangitis or cholangiolitis may produce liver damage and affect other organs detrimentally, it is important to try aureomycin or some closely related antibiotic in *Proteus Vulgaris* infections before irreversible pathological damage is produced.

REFERENCES

- Duggar, B. M.: *Ann. New York Acad. Sc.*, 51:177 (Nov. 30) 1948.
- Wong, S. C. and Cox, H. R.: *Ann. New York Acad. Sc.*, 51:290 (Nov. 30) 1948.
- Anigstein, L., Whitney, D. M., and Bennison, J.: *Ann. New York Acad. Sc.*, 51:306 (Nov. 30) 1948.
- Chandler, C. A. and Bliss, E. A.: *Ann. New York Acad. Sc.*, 51:221 (Nov. 30) 1948.
- Schoenbach, E. B., Bryer, M. S., and Long, P. H.: *Ann. New York Acad. Sc.*, 51:267 (Nov. 30) 1948.
- Schoenbach, E. B. and Bryer, M. S.: *J.A.M.A.*, 139:275, (Jan. 29) 1949.
- Finland, M., Collins, H. S., and Wells, E. B.: *New Eng. J. Med.*, 240:241 (Feb. 17) 1949.
- Kneeland, Y., Rose, H. M. and Gibson, C. D.: *Am. J. Med.*, 6:41 (Jan.) 1949.
- Spink, W. W., Braude, A. I., Castaneda, M. R. and Goytia, R. S.: *J.A.M.A.*, 138:1145 (Dec. 18) 1948.
- Knight, V., Ruiz, Sanchez, F., Ruiz, Sanchez A., and McDermott, W.: *Am. J. Med.*, 6:407 (April) 1949.
- Long, P. H.: *Am. J. Pharm.*, 121:64 (Feb.) 1949.
- Dowling, H. P., Lepper, M. H., Sweet, L. K., and Brickhouse, R. L.: *Ann. New York Acad. Sc.*, 51:241 (Nov. 30) 1948.
- Harrell, G. T., Meads, M., and Stevens, K. M.: *South. M. J.*, 42:4 (Jan.) 1949.
- Collins, H. S., Paine, T. F., Jr., and Finland, M.: *Ann. New York Acad. Sc.*, 51:231 (Nov. 30) 1948.
- Long, P. H., Schoenbach, E. B., Bliss, E. A., Bryer, M. S., and Chandler, C. A.: *California Med.*, 70:157 (March) 1949.
- Ross, S., Burke, F. G., Rice, E. C., Schoenbach, E. B., Biehoff, H. and Washington, J. A.: *Clin. Proc. Child. Hosp.*, 4:315 (Nov.) 1948.
- Nichols, D. R. and Needham, G. M.: *Proc. Staff Meet. Mayo Clin.*, 24:309 (June 8) 1949.
- Rose, Harry M. and Kneeland, Yale: *Am. J. Med.*, 7:532 (Oct.) 1949.
- Herrell, W. E. and Heilman, F. R.: *Proc. Staff Meet. Mayo Clin.*, 24:157 (March 30) 1949.
- Frobisher, Jr., Martin: *Fundamentals of Bacteriology*, W. B. Saunders, Phila., 4th ed., 575, 1949.
- Levinson, S. A. and MacFate, R. P.: *Clinical Laboratory Diagnosis*, Lea and Febiger, Phila., 3rd ed., 670, 1946.
- Colp, Ralph: *Bull. New York Acad. Med.*, 20:203 (April) 1944.
- Held, I. W. and Goldbloom, A. Allen: *Jaundice, Classification, Diff. Diagnosis and Treatment*, *Internat. Clin. I*, Series 3, 71, 1940.
- Twiss, J. R. and Carter, R. F.: *N. Y. State J. Med.*, 48:45, (Oct. 15) 1948.
- Held, I. W.: Sepsis (Unpublished data), 1947.
- Garbat, A. L.: *Monograph Rockefeller Inst.*, 16:17-19, p. 102, 103, 1922.
- Gotschlich, E.: *Microbes in Bile*, In *Kolle-Wassermann's Handb.* 1:290, p. 102, 1929.
- Sobotka, Harry: *Physiological Chemistry of the Bile*, Williams and Wilkins Co., Balt., pg. 102, 1937.

INCOMPLETE OBSTRUCTION OF THE SMALL INTESTINE

ALEXANDER STRELINGER, M. D., M.Sc. (SURG.) F. A. C. S., Elizabeth, N. J.

THE SYMPTOMATOLOGY of commonly encountered complete intestinal obstruction is well known, the cardinal symptoms being abdominal pain, colic and vomiting. Radiological examination is usually diagnostic. An incomplete or partial obstruction however does not produce clear symptoms. Six cases of partial obstruction of the small intestinal tract are reported to bring into focus four points: 1. the symptoms were not definite and varied a great deal; 2. the obstruction escaped roentgen diagnosis; 3. clinical signs in some of them permitted to diagnose probable obstruction; 4. the non-malignant cases obtained permanent relief of their symptoms by surgical removal of the obstruction. All six cases were operated.

CASE REPORTS

Case 1. Male patient, 31 years old, seen in July 1935. Past history: bloating and distention, occurring after meals, present for four years. Chief complaint: acute abdominal pain located into the right lower quadrant. Patient was hospitalized with the diagnosis of possible acute appendicitis. After one day of observation the patient was released, because acute symptoms subsided. The patient was not seen until April 1942. Then he reported for examination. He continued after his hospitalization in 1935 to have distention and abdominal pain. In 1938 he underwent an appendectomy because his complaints were attributed to appendicitis. He experienced no relief; pain, distention and colics continued. He had to belch a lot. There was no vomiting. He usually had one

formed bowel movement daily. He gained weight gradually over a number of years, his weight when examined was 220 lbs. The appetite was good. At times he had urinary frequency. Physical examination, gall-bladder x-ray and a gastrointestinal study were not diagnostic. He was hospitalized. The diagnosis of probable intestinal obstruction was made on account of colicky pain and intermittent abdominal distention; exploration was advised. Patient left against advice. His complaints continued unabated. He was re-hospitalized in June 1942 and an exploratory was done. A mass of the size of a small grapefruit was found with 2/3 of its substance to the right, with one third to the left of the midline in the pelvis; a loop of the ileum was solidly bound down to it and this loop was angulated. Attempt to free this loop was not successful. An ileotransversostomy was done, the mass was not removed. Uneventful recovery followed. The patient was relieved of his complaints. He was seen in 1945, his original complaints remained relieved.

As it was not known what is the nature of the pelvic tumor, he was rehospitalized again in September 1942. On laparotomy it was found that the tumor consists mostly of fat and it is transversed by many small channels containing feces. The diagnosis of peridiverticulitis was made; the incision into the tumor mass itself closed. The adherent ileal loop could not be freed. Following this operation the patient developed a fecal fistula. Barium enema disclosed the fistula, but no diverticula. An attempt of direct closure of the fistula, following an intensive course of weight reduction, failed. Later on a colostomy was done by another surgeon on this patient, it resulted in closure of the intestinal fistula, thereafter the colostomy was closed. As far as it is known this patient still has an obstructed, and shortcircuited ileal loop.

Case 2. Male patient, 46 years old, was seen in June 1941. He had the past history of headaches since early childhood. Six months prior to the examination he had three bilious attacks in short succession which were relieved by vomiting. His main complaint was pain around the umbilicus of one week duration. He also mentioned that he gained some weight; that due to gain in weight his abdomen became so large that his trousers



Fig. 1. Case 1. Operative findings: Peridiverticulitis of the sigmoid, an ileal loop firmly adherent to the inflammatory mass. Four hour film showing filling defect in the right lower quadrant, air in the adjacent ileal loop. These features were seen only on this film; others showed apparently normal filling.

Read at the Standardization Meeting of the St. Elizabeth Hospital, Elizabeth, N. J. on Nov. 8, 1949.

Submitted Dec. 29, 1949.

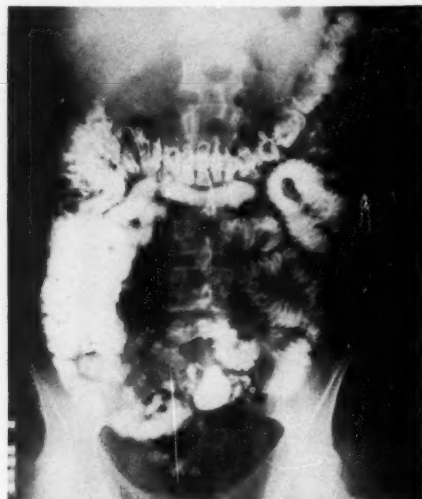


Fig. 2. Case 2. Chronic appendicitis. A loop of the ileum was adherent to the appendix with angulation. 4 hour examination.

AMER. JOUR. DIG. DIS.

did not close around the waist, the ends of the waistband were four inches apart. There was no abdominal pain, except that around the umbilicus, no colic, no vomiting, no belching, no anorexia. He had usually one bowel movement daily, no change in bowel habits. He noticed that he drinks more water and he urinates more often. On physical examination subacute cellulitis around the navel and a considerably distended abdomen were the physically significant findings. The gain in weight was 8 lbs. and did not seem to account by itself for the increase of the girth of the abdomen. The patient was immediately hospitalized and placed on Wangensteen suction. In two days time his abdomen was deflated, and he had no trouble to close the waistband of his trousers. The subacute cellulitis continued. A progress meal study was done and nothing significant found. Meanwhile his distention returned. He was operated upon on July 1, 1941 with the diagnosis of inflammatory lesion causing intestinal obstruction. The inflamed and hard tissue at the navel was surrounded with two semi-elliptical incisions and the whole thickness of the abdominal wall removed. Contrary to expectation there was nothing found connected with the inflamed abdominal wall. Careful inspection of the intestinal tract revealed that the ileum about six inches distant from the ileocecal angle was adherent to the appendix, and it was sharply angulated. The loop was freed, and appendectomy was done, and the abdomen closed. Uneventful recovery followed. The patient did not experience any further distention, nor was any found on follow-up examination. Two months after operation he volunteered the information that his headaches of long standing ceased immediately after the operation. Recently, after a period of eight years following the operation, he was questioned about this, he stated that the headaches never returned.

Case 3. Male patient, 51 years old, was seen in November 1941. He always felt well until May 1941. Then he had influenza. He failed to pick up after it, and he felt very weak. This was his main complaint. He also had bloody urine for a day or so in September 1941; at times he felt nervous in his stomach; constipation developed. Initially there was no abdominal pain, no colic, no backpain, no belching, no vomiting. The left lower quadrant seemed to be distended, the patient stating that this was present for a long time. There was loss of weight, anorexia and frequency of urination present. On examination he looked poorly nourished and very pale. The spleen was palpable and hard; the left lower quadrant was protruding and felt like a large cyst. No masses, tenderness or rigidity otherwise. Amongst various studies the feces repeatedly showed a strongly positive test for occult blood on meat free diet; the blood hemoglobin was 9 grams per 100 cc.; gastrointestinal series showed a rapid passage of the bar-

ium through the small intestinal tract reaching the cecum within an hour; flat film of the abdomen showed peculiar scattered calcifications in the left kidney region; retrograde pyelogram an upward and lateral displacement of the left kidney pelvis and distortion of the same. The patient was hospitalized. On account of definite kidney pathology and repeatedly positive test for occult blood in the feces some kind of malignancy was suspected involving both the urinary and the intestinal tracts. After a few days of hospitalization, abdominal pain set in and the lower half of the abdomen became somewhat rigid. On November 25, 1941, the patient was operated upon. Foul smelling pus was found in the lower half of the abdomen. Pieces of broken down tissue were floating freely in the abdominal cavity. A mass of the size of an orange was located in the right lower quadrant, this involved a loop of the ileum. An opening was in the mass, it led into the lumen of the involved ileal loop, pus, fecal material and gas exuded through this opening. Tumor was found to be present within the lumen of the involved and perforated ileal loop. Another mass, lengthy in shape, about one by four inches large, was located in front and partly to the left of the vertebral column. No attempt was made at more complete exploration. A catheter was inserted into the open ileal loop, the gut closed around it as much as possible, omentum was wrapped over the loop and around the catheter, drains were placed into the abdomen, and this then closed. The patient expired on the seventh post-operative day. On autopsy a clear cell carcinoma of the left kidney was found. This metastasized into the mesenteric lymph-nodes; one of these invaded by continuity the ileum.

Case 4. A 61 year old male was seen in March 1943. 35 years prior to that he was operated upon for appendicitis and right inguinal hernia, appendectomy and hernial repair were done. He was treated for ulcer of the stomach for many years and he always was low in weight. He lost about 6 lbs. during the month preceding the examination. More recently he had the feeling that he can not empty his bowels, though he had a small bowel movement every day. At times he had slight colicky pain. His appetite was decreasing for some time. There was no belching, no vomiting, no distention, no urinary symptoms. Physical examination showed a poorly nourished male patient. There was some rigidity over the right lower quadrant, and also an indefinite impression of a small mass. Otherwise the physical examination was not significant. He was hospitalized and a gastrointestinal series was done. The report on the series was possible prepyloric ulcer. Due to the loss of appetite and of the weight, to the colicky pains and to the indefinite impression of a mass the preoperative diagnosis

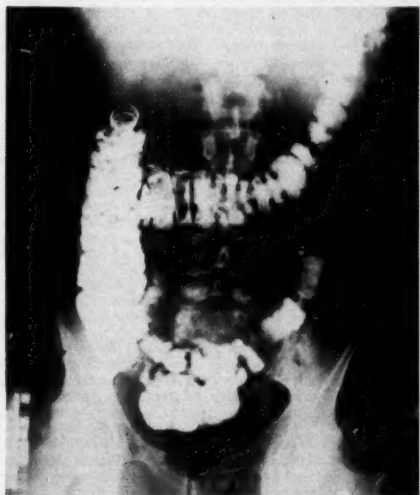


Fig. 3 Case 2. 5 hour examination.



Fig. 4. Case 3. Clear cell cancer of the left kidney (Hypernephroma) with metastasis to retroperitoneal lymph nodes; one node invaded the ileum.

of abdominal neoplasm was made. The patient was operated upon on April 5, 1943. A retroperitoneal tumor of the size of an orange was found in the right lower quadrant. The iliac vessels passed through the tumor. A loop of the ileum was tacked down to this tumor and it was sharply angulated. The tumor consisted of a multiloculated structure, the dividing walls of which seemed to be normal fibrous tissue, the contents of the pockets was a semisolid, uniform, caseous mass. The cecum was mobilized, the peritoneum and the ileal loop above it was peeled off the tumor and thereby the mass well exposed. Following one of the dividing septa the tumor was incised and divided until the iliac vessels were reached; then the vessels shelled out of the tumor and dislodged; then the whole tumor mass removed. The raw surface was peritonealized by replacing the cecum and the peritoneum. The abdomen was closed. Uneventful recovery followed with relief of colicky pain and also of the feeling of not being able to empty the bowels; the appetite improved and the patient gained weight. The pathological report on the excised tumor was: Clear cell carcinoma as seen in clear cell carcinoma of the kidney. As during the operation there was no connection seen between the tumor and either of the kidneys, this report was surprising. Retrograde pyelogram done postoperatively did not reveal unusual features on the kidneys. The tumor was thought to be an atypical one. By November 1943 the patient had pelvic pain and an indefinite mass was found by rectal examination above the prostate. He was referred to the Memorial Hospital in New York, N. Y. There he was subjected to a bilateral orchidectomy, and it was heard that this was followed by temporary improvement. The patient moved to Florida; it was heard that he succumbed to the disease before the end of 1944.

Case 5. The first examination of this male patient referable to his abdominal complaints in his fatal disease was in June 1947. He then was 45 years old. His previous history included stomach complaints of many years standing, for which he was examined by various physicians; a right inguinal hernia repair done under spinal anesthesia in 1943 followed by persisting headaches still present in June 1947; progressive constipation. More recent complaints were: abdominal distention, and sour and bitter belching, of at least six months duration; abdominal pain, intermittent colicky pain, and loss of appetite of somewhat shorter duration; no urinary symptoms. His blood pressure was 88 over 64, his weight 186 lbs. Physical examination otherwise was not contributory. He was advised to be studied; but he returned only in August 1947. He lost by that time 9 lbs.; his symptoms were more intense and at times he had nausea. On physical examination the blood pressure was 120 over 80; a tumor of the size of an orange was felt in the epigastrium, this region was very tender to pressure. During the next two weeks various studies were done; on repeated physical examinations rigidity was found over the epigastric region and the upper half of the abdomen; this seemed to obscure the previous finding of the tumor. The only radiological finding of significance was the displacement of the stomach and of all intestinal loops from the midabdomen.

On September 15, 1947 an exploration was advised. The patient was very hesitant. Therefore the suggestion was made that he should obtain additional consultation. He then was not seen until December 19, 1947. On that date he returned and presented the written findings of a diagnostic clinic, to which he had been referred in September by another physician. Amongst the numerous studies carried out at that clinic and reported upon, a note about the physical examination stated that rigidity was found over the abdomen, no masses reported; a gastro-intestinal fluoroscopic examination showed the stomach as being of normal size and location, with normal peristalsis and antrum formation; no mention about the intestinal tract; complete blood count and sternal bone marrow studies showed a peripheral polynucleosis and good sternal activity, noting that this picture does not suggest myeloma or leukemia; nor is there any evidence of malignancy; an increased sedimentation rate was noted. A neuropsychiatric study concluded that there is an anxiety state present with reactive depression, due to emotional conflict; psychotherapy was advised. The date of this psychiatric study was October 23, 1947, the date of the main body of the report was November 10, 1947. Physical examination on December 19, 1947 disclosed a tumor in the abdomen about 20 to 25 cm. in diameter; the patient's weight was down to 156 lbs. Several more radiograms were made of the gastrointestinal tract, and they showed that the displacement of the stomach and of the intestinal loops is more

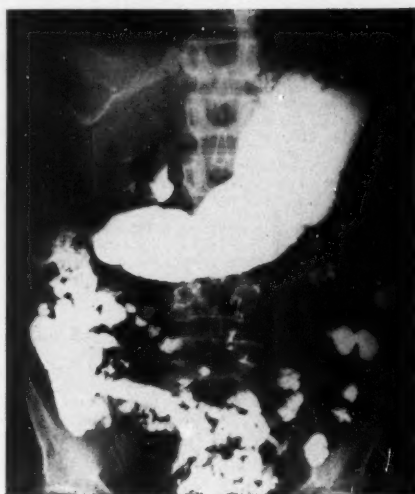


Fig. 5. Case 4. Atypical clear cell cancer (Hypernephroma) surrounding the iliac vessels in the right lower quadrant of the abdomen. An ileal loop was adherent but not invaded.

marked than it was three months previously. The patient was hospitalized and laparotomy was done on Dec. 30, 1947. The essential finding was a retroperitoneal tumor reaching from the left to the right gutter, passing across the abdomen between the aorta and the pancreas; seemed to have a general antero-posterior thickness of about 10 cm., and had no pedicle. The left kidney seemed to be enveloped in the tumor; a separate mass was felt in the right lumbar region, which may have been a normal kidney. Several small intestinal loops were tied down to the tumor and were markedly angulated. Realizing the hopelessness of the condition several biopsies were taken and the abdomen closed. The pathological report was lymphoblastic lymphosarcoma. Uneventful recovery followed until the eleventh postoperative day, when the patient attempted to hang himself on a curtain rod; it broke, the patient fell onto the floor and eviscerated. He was resutured, but he expired on the thirteenth postoperative day.

Case 6. A 38 year old female was seen in August 1949. Her past history included one normal pregnancy and two abdominal operations; these were done 9 and 10 years prior to the examination, they were appendectomy and a pelvic operation of unknown nature to the patient. Her complaints began in March 1949. Her abdomen enlarged. First she was thought to be pregnant, but meanwhile this was ruled out. Abdominal pain, colicky pain, pain in the back and constipation developed; she gained about 12 lbs. in 5 months; at one time there was urinary frequency. There was no belching, no vomiting, no anorexia. Physical examination showed a fairly well nourished patient; a midline and a right lower abdominal postoperative scar; the abdomen was distended, to a higher degree on the left than on the right side. There was generalized tenderness over the abdomen; no rigidity nor masses. During the subsequent studies the patient received castor oil twice preparatory to various radiological examinations; on both occasions this resulted in large evacuation followed by lessening of the distention and temporary relief of complaints of short duration. Amongst the various studies neither the barium enema nor progress meal showed significant findings. On the basis of distention, which temporarily yielded to purge, abdominal pain and colicky pain, the diagnosis of probable intestinal obstruction was made. On Sept. 26, 1949 the patient was operated upon. The only positive finding was a high ileal loop attached to the posterior abdominal wall, the point of attachment consisting of a strong adhesion, and the loop was very sharply angulated. This loop was released, its raw surface peritonealized and the abdomen closed. Uneventful recovery followed. Thus far

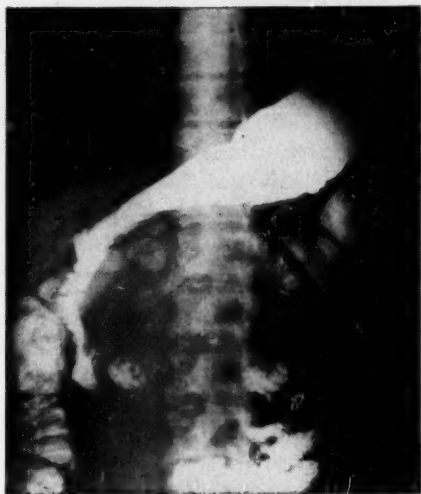


Fig. 6. Case 5. Retroperitoneal lymphoblastic lymphosarcoma displacing stomach and jejunum. Several jejunal loops adherent. The pancreas was not involved.

the patient has complete relief of abdominal pain, colicky pain and pain in the back. Her abdomen returned to normal size. She has one or two voluntary bowel movements daily.

DISCUSSION

A partial obstruction of one or more small intestinal loops was found on operation in these six cases. There were no diagnostic x-ray findings referable to small intestinal obstruction in any of them; vomiting occurred in only one of them, and in that one it occurred several months prior to the operative relief and also ceased prior to it. Distention of either the whole abdomen, or part of the abdomen was present in five out of the six cases, the four surviving ones obtained good relief of it. Constipation was present in four out of the six, also relieved. It seems interesting that the two patients not having this symptom had marked distention. It appears, that the distention was caused by retarded intestinal contents; increased peristalsis propelling enough of it through the narrowed point to result in daily bowel movement. Anorexia was not present in any case that had no underlying malignancy, and these non-malignant cases, for unknown reason, gained in weight. Conversely the malignant cases lost weight. The non-malignant cases obtained, following operation, permanent improvement of all symptoms. In view of absent radiological findings a quick review of the symptoms leading to operative indication is in order. In the first case the preoperative diagnosis of probable obstruction was made because of colicky pain and intermittent distention. In the second, obstruction was thought to be present because of the marked distention temporarily subsiding on Wangenstein suction. In the third, malignancy of the intestinal tract and also that of the urinary tract was suspected because of the consistent markedly positive test for occult blood in the feces and the radiological findings pertinent to the urinary

tract. In the fourth case, abdominal neoplasm was the preoperative diagnosis because a mass was felt indefinitely and its location was painful. In the fifth, by the time of the operation there was a huge palpable tumor; but exploration was advised several months before it was carried out, because the small tumor observed once, then the superseding abdominal rigidity, tenderness and loss of weight were suggestive of neoplasm. In the sixth case we again find distention, temporarily subsiding to purge, suggestive of obstruction.

The report of the six cases and the discussion thus far account for the four points which originally were intended to be brought into focus.

The difficulty encountered in these cases was chiefly that of the diagnosis. There are numerous reports in the literature stating that the diagnosis of incomplete obstruction of the small intestinal tract often is difficult. Kiefer (1) stated, that " . . . certain limitations of roentgenologic diagnosis must be kept in mind. Since narrowing of the lumen of the small bowel may cause no delay until obstruction is almost complete, intermittent small bowel obstruction, particularly when caused by bands of adhesions, may not be evident roentgenologically unless the examination is made in the presence of obstruction. In suspicious cases, if possible, the patient should be examined during an attack even if only by plain film of the abdomen, in the upright position, so as to show fluid levels in the distended loops." A method of radiological study of the small intestines is the bowel enema. It is usually credited to Schatzki, but he, (2) in his original publication suggests that Pesquera was probably the first worker to suggest this method. It briefly consists of passing a tube with its tip past the pylorus, and then filling through this tube the entire small bowel tract with barium suspension by continuous stream. It is claimed that details can be identified by this method not done so by the usual routine. This method however does not seem to be suited for office investigation. Further it does not seem probable that it will show the cause of an intermittent or relative small intestinal obstruction, unless used during an acute phase as mentioned by Kiefer. An entirely different approach was used by gastrointestinal physiologists: that was the measuring of the intestinal pressure. Abbott and his co-workers (3) described an instrument suitable for such work; in their own experiments pressures were read in the jejunum at a level above an artificial obstruction and significant rise in the mean pressures was found. But in the opinion of the authors themselves, the instrument is like an old Swiss watch; it takes the original makers to repair it when it breaks down.

Considering therefore these reports and whatever was gleaned from the literature it would seem that in a certain number of cases of relative small intestinal obstruction, consistent observation of the patient, at times over long periods and correlation of all clinical and laboratory data will lead to diagnosis not obtainable by routine studies. The clinical symptoms, like colicky pain, intermittent distention, deflation by cathartic or by indwelling tube, constipation and occult blood in the feces as a laboratory examination must be properly evaluated. When so done, the conclusion obtained by it must convey the same sense of reality to the clinician as would the presence of a persistent radiological defect.

REFERENCES

1. Kiefer, Everett, D.: Diagnosis of disorders of the small and large intestine. *New York State Journal of Medicine*, 44, 2342, 1944.
2. Schatzki, Richard: Small intestinal enema. *American*

- Journal of Roentgenology*, 50, 743, 1943.
3. Abbott, W. O., H. K. Hartline, J. P. Hervey, F. J. Ingelfinger, A. J. Rawson and L. Zetzel: Intubation studies on the human small intestine. *Journal of Clinical Investigation*, 22, 225, 1943.

DEMONSTRATION OF A TUMOR INVOLVING THE PANCREAS THROUGH THE USE OF DUODENAL DRAINAGE AND THE INTRAVENOUS INJECTION OF SECRETIN

N. R. BOTHEREAU, M. D., F. H. DRAPER, M. D., AND G. E. CIBES, M. D., San Francisco, Calif.

IT IS WELL KNOWN that the diagnosis of tumors involving the pancreas is often difficult, especially in cases in which jaundice is absent. The following case study presents an approach to this problem and illustrates the methods by which it is sometimes possible to diagnose such neoplasms. The procedures used are well-established methods which, when coordinated, can yield important information to the physician. They involve chemical and cytologic study of the secretion obtained by duodenal drainage, in particular the secretion obtained after intravenous injection of the hormone Secretin. The following case illustrates the application of the principles involved.

CASE HISTORY

The patient, an 89-year-old woman, gave a history of right upper quadrant abdominal pain of one month's duration. Jaundice developed two weeks later, and at that time drainage from a fistulous tract orifice in an old cholecystic surgical scar (from an exploratory operation for gall stones 45 years before) was noted. Examination revealed a thin, jaundiced elderly woman, with a fistulous tract orifice at the right costal margin, but without other significant physical findings. The urine contained some bile. Other laboratory findings revealed the following: serum albumin, 3.4 Gm. %; globulin, 3.5 Gm. %; icterus index, 50 units; thymol turbidity, 2 units; cephalin flocculation, 2 plus. One week later the icterus index was 113 units.

Radio-opaque dye was injected into the fistulous tract and x-ray studies done, but results were inconclusive.

Duodenal drainage was then done, by means of a double lumen tube, with one lumen in the stomach and one in the duodenum. The contents from these two sources were continuously aspirated so that there would be no mixing of secretions, thus insuring that any secretion obtained from the duodenum was truly representative of the duodenal contents. For convenience of insertion, an infant-sized tube (12 F) with a gold

tip weighing 3 grams was used (1). Fasting specimens of the secretion were obtained for chemical and cytological study. Secretin was then injected intravenously in a dosage of one clinical unit per kilogram of body weight.* Following the injection, specimens were again taken over 20 minute periods. That portion of each of the pre- and post-Secretin specimens intended for cytologic study was immediately placed in fixing fluid and prepared for paraffin sections (2).

The chemical determinations on the secretion are shown in Table I. It is of interest to note the exocrine function of the pancreas in consideration of the pathologic process involved.

When considered in comparison with the control group, the patient studied seems to have had a substantial, probably normal, pancreatic exocrine function at the time of this study, 11 days before death.

Cytologic studies of paraffin sections of the coagulated and filtered post-Secretin specimen revealed clumps of neoplastic cells. These cells presumably came from the pancreas (Figure 1).

The patient followed a downhill course and expired 11 days after the present study was done. An autopsy revealed an adenocarcinoma of the gall bladder and extrahepatic biliary tract, with metastases in the head of the pancreas (Figure 2) and elsewhere in the body. The ampulla of Vater and the duodenum, on section, showed a marked mucosal necrosis and degeneration but no invasion by the tumor.

The important point in this particular case is that it was possible to demonstrate carcinoma tissue in material aspirated from the duodenum following the intravenous administration of Secretin.

SUMMARY

1. A case is described in which pancreatic function and histocytology were studied by the use of duodenal drainage before and after intravenous injection of Secretin.

2. It was possible to demonstrate, by this method, an essentially normal exocrine function and the presence of carcinoma tissue.

3. It is suggested that the method described may be of aid in the diagnosis of carcinoma of the pancreas,

TABLE I
CHEMICAL STUDIES OF DUODENAL DRAINAGE
Secretin collected during the 20 minutes before injection of Secretin Secretin collected during the 20 minutes following the injection of Secretin

Patient	5 Controls			Mean	Patient	5 Controls			Mean
	Max.	Min.				Max.	Min.		
Volume in ml.	12.5	15	3	10	58.0	61	31	45	
pH	7.9	8.0	7.6	7.8	8.0	8.4	7.7	8.1	
Alkali*	0.010	0.046	0.010	0.023	0.048	0.082	0.020	0.057	
Trypsin**	183	245	34	127	92	86	48	58	
Amylase***	93	218	46	101	65	105	43	69	

*Meq./ml. determined by back-titration after boiling with standard HCl.

**Anson method, using hemoglobin substrate.

Tabulated values $\times 10^{-4}$ = enzyme liberating chromogenic substances equal to 1 meq.

tyrosine per min. per ml. of juice.

***Willstatter method. Tabulated values $\times 10^{-3}$ = first order reaction constant.

From the Divisions of Medicine, Pathology, and Pediatrics, University of California School of Medicine, San Francisco.

Submitted May 19, 1950

*We are indebted to John Wyeth & Co. for a supply of the Secretin.



Fig. 1. Neoplastic tissue in paraffin section prepared from specimen obtained from the duodenum after intravenous Secretin was given. (x 960)

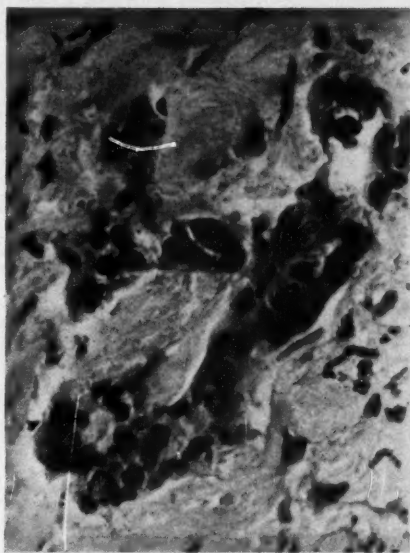


Fig. 2. Section of specimen obtained from the pancreas at autopsy. (x 960) Compare with Fig. 1.

either primary or metastatic, as well as in the diagnosis of other pancreatic conditions, both functional and structural.

REFERENCES

1. Gibbs, G. E.: Some Diagnostic and Therapeutic Techniques in Cystic Fibrosis of the Pancreas, *Calif. Med.*, 69:341 (Nov.) 1948.
2. Botheranu, N. R.: The Use of Paraffin-Embedding Methods in the Cytologic Study of Various Bodily Secretions, *Am. Journ. Med.*, VIII, 6, 1950, 733-737.

ABSTRACTS ON NUTRITION

MAXCY, K. F.: *Relation of nitrate nitrogen concentration in well water to the occurrence of methemoglobinemia in infants.* (U. S. Armed Forces Med. J., 1, 9, Sept. 1950, 1007-1015.

A review of our knowledge to date indicates that methemoglobinemia in infants using well water is not uncommon, and that in Minnesota the disease carried a 10 per cent case mortality and an incidence of 1 case per 1,000 live births. The exact reasons for individual susceptibility are not known, although infants under 6 months of age are chiefly affected and adults are unaffected. The exact chemical nature of the water producing the disease likewise is not understood. A survey of the whole country by a team of experts (epidemiologist, pediatrician, sanitary engineer, biochemist and bacteriologist) is urgently needed.

SHIELS, D. O.: *Influence of lead absorption on the ratio of large to small lymphoid cells.* (Med. J. Australia II, 6, Aug. 5, 1950, 205-211).

Shiels discusses the results of determinations of the ratio of monocytes plus large lymphocytes to small lymphocytes in a series of over 400 persons employed in various lead trades. Absorption of lead causes an increase in this ratio of monocytes plus large lymphocytes to small lymphocytes. In cases of lead poisoning this ratio falls again to within the range of the ratio for non-exposed persons. If the ratio falls to less than 2.0, lead poisoning is imminent, if not already present. Recovery from lead poisoning is accompanied by a rise in the ratio to above 2.0 in the early stages. In the later stages of recovery the ratio falls again to the range of ratios of

non-exposed persons. This ratio determination forms a valuable guide to the prevention and diagnosis of lead poisoning.

MODERN, F. W. S., LEIK, D. W. AND RAPAPORT, S.: *Nutritional heart disease.* (Amer. Pract. and Dig. Treat., 1, 10, Oct. 1950, 1044-1049).

Obesity embarrasses the heart, starvation weakens it and renders it smaller. Vitamin E has not been proved to affect coronary disease favorably. The beriberi heart may be found in America. The patients appear well nourished: the heart is large and baggy and dilated and tends to harbor mural thrombi, but Blankenhorn's 8 criteria for diagnosis seldom can be found present in any single case. The response to thiamin therapy is poor in cases where the deficiency has been extreme or of long duration. In the two cases of beriberi heart herein presented, edema was a marked feature. Chief reliance was upon digitalis but both cases terminated fatally.

SEVRINGHAUS, E. L., COHEN, S., GANS, R. H. AND SUNG-NIEN LI: *Nicotinamide therapy of lingual changes in tuberculous patients.* (Am. Rev. Tuberculosis, 62, 4, Oct. 1950, 360-373).

25 patients with advanced active pulmonary tuberculosis who showed gross lingual evidence of most of the abnormalities commonly ascribed to niacin deficiency were treated by large doses of nicotinamide. Of 13 such cases, treated for an average of 204 days, 6 showed reduction in redness and swelling and regeneration of papillae. In 2 patients no change occurred and in 5 the glossitis progressed. Similar cases treated with placebos showed about the same percentage of improve-

ment. Control of the tuberculosis is essential in achieving lingual improvement. Niacin is a factor in glossitis, but balanced and complete nutritional therapy is essential, particularly a high protein intake. The B-complex ought to be administered as such, rather than its isolated components.

TUTTLE, W. W., DAUM, K., MYERS, L. AND MARTIN, C.: *Effect of omitting breakfast on the physiologic response of men.* (J. Am. Diet. Assn., 26, 5, May 1950, 332-335).

Omitting breakfast produced very definite increase in tremor magnitude and reduction in maximum work output in 10 men examined and, in 3 of them, an increase in choice reaction time. The reactions which most of them experienced irregularly were dizziness, nausea and vomiting. Women are not nearly so much affected by omitting breakfast.

JEANS, P. C.: *Application of nutrition research to everyday practice.* (Am. J. Dis. Child., 80, 3, Sept. 1950, 363-369).

Although there is a time lag between nutritional discoveries and their practical application, the increase in life expectancy is partly due to nutritional advance and at present more progress is being made in nutrition than in all other forms of medical therapy. The adult requirements of individual amino acids is now known quantitatively. The importance of protein in anemia, and the relationships among vitamin B₁₂, folic acid and the utilization of tyrosine are now clearer. Body length is significantly greater now than 30 years ago. Babies are being fed much more abundantly. The necessity of fortifying human milk is recognized. Human milk is no longer considered better than cow's milk for babies. Perhaps adult hypertension may depend upon an infantile phase of malnutrition.

MAY, C. D., NELSON, E. N., LOWE, C. U. AND SALMON, R. J.: *Pathogenesis of megaloblastic anemia in infancy: an interrelationship between pteroylglutamic acid and ascorbic acid.* (Am. J. Dis. Child., 80, 2, 191-206).

Nutritional experiments in monkeys indicated that a chronic deficiency of ascorbic acid leads to a deficiency of pteroylglutamic acid or some difficulty in the metabolism of pteroylglutamic acid or related compounds which results in a megaloblastic pattern in the marrow. In infants fed milks which supply adequate vitamin C, megaloblastic anemia has disappeared. Vitamin B₁₂ is unable to convert a megaloblastic marrow to normal when folic acid or related compounds are unavailable. In treating megaloblastic anemia in infants, the ascorbic acid intake must first be assured, and beyond this, folic acid is

unquestionably superior to vit. B₁₂. Crude liver extract by daily intramuscular injection early in treatment also is recommended.

MILLAR, E. L. M. AND POWNALL, M.: *Food poisoning in Sheffield in 1949.* (Brit. Med. J., Sept. 2, 1950, 551-553).

Four outbreaks of food poisoning in Sheffield during 1949 were associated with *staph. aureus* infection of the hands of the food preparer. Before concluding that an outbreak of food poisoning is due to *staph. aureus*, a strain of a type generally associated with food poisoning should be isolated from a number of victims or from one or more victims and food. Such evidence was obtained only in the first 2 outbreaks described. In every outbreak, speedy notification and immediate investigation of the hands which prepared the food are essential to success.

BRINKMAN, G. L. AND PRIOR, I. A. M.: *Chronic beri-beri heart disease.* (New Zealand Med. J., XLIX, 271, 266-271).

A case is reported in which congestive heart failure with myocardial and endocardial fibrosis, mural thrombi and cardiac hypertrophy of probable nutritional origin, developed 7 years after the period of most severe dietetic deficiency. Such late-occurring cases result from long-continued mild deficiency of vit. B₁ and they do not respond to treatment with thiamine. The present case developed terminally a series of pulmonary infarcts. The EKG showed intraventricular block and some ventricular extrasystoles. The heart was markedly enlarged and the patient died of congestive failure. In such cases, reliance must be placed on digitalis, but the extensive cardiac damage, due probably to a defect of muscle metabolism, suggests a poor prognosis.

GORDON, J. E. AND LERICH, H.: *Epidemiology and nutrition surveys.* (Nutrition Reviews, 8, 8, 225-227).

Epidemiologic studies were among the earliest in nutrition. Spectacular epidemics, rivaling those of infectious origin, gave rise to the belief that they were communicable processes. Just as infectious agents so long dominated medical thought about communicable diseases, so the vitamins have been over-emphasized in the death, defect, and disability associated with nutritional disorders. Epidemiologic study of disease in the field uses three principal scientific disciplines,—those of clinical medicine, of the laboratory and of biostatistics. This holds equally in application to nutritional disease. In nutrition surveys, the chief difficulty has been in defining a normal value. Experiments should be designed in advance of operations and aimed at a definite problem.

EDITORIAL

CANCER OF THE STOMACH AND PERNICIOUS ANEMIA

WEINBERG, IN THE PRESENT issue of this Journal, makes a first class contribution to the study of the problem of gastric carcinoma occurring in patients with Addisonian pernicious anemia. Many observers have found that since the liver era of pernicious anemia began about 1926, a dangerously high incidence of cancer of the stomach occurs in the disease. Although chronic gastritis has been regarded as the common link, Weinberg demonstrates from gathered statistics and special studies that although there is a physiological delinquency in the secretion of gastric juice in most persons suffering from pernicious anemia, there is actually no gastritis. He logically concludes that cancer must develop in the pernicious anemia stomach either because patients live longer than formerly or because they are sensitive to a carcinogenic agent known to be present in liver extracts. The fact that prior to the liver-therapy era these patients seldom developed gastric carcinoma appears to strengthen Weinberg's conclusion.

As yet there is no evidence to indicate whether the

use of crystalline vitamin B₁₂ will or will not reduce or abolish the abnormally high incidence of cancer of the stomach in victims of Addisonian anemia, but it is a point of great interest which may require possibly an additional 3 or 4 years for its elucidation. It is possible that some physicians might be able to furnish a series of cases who have been maintained on ventriculin, and such a report, with special attention to the cancer incidence, would help toward an ultimate conclusion. Although a few patients do better on ventriculin than on parenteral treatment with liver extracts, most of them rebel against the inconvenience of taking the necessarily large oral doses.

Until the present uncertainty with respect to the cause of gastric cancer in pernicious anemia has been done away with, it remains the duty of every physician treating the disease to be on guard against the development of this serious lesion of the stomach. It has been said that an annual, carefully-conducted radiological examination of the stomach might be expected to detect about 90 percent of such neoplasms at a stage when they are still amenable to radical surgical cure. Gastroscopy ought also to be employed annually when feasible.

BOOK REVIEWS

A SYLLABUS OF LABORATORY EXAMINATIONS IN CLINICAL DIAGNOSIS. Thomas Hale Ham, 496 pages, Harvard University Press, Cambridge, Mass., 1950, \$5.00.

Some 34 authorities have combined their efforts to produce an unusually thorough and critical description of common clinical laboratory examinations. Although examination of the blood assumes a primary position, sections equally valuable are devoted to the urine, the kidney function, the gastrointestinal tract, the sputum, metabolic diseases, and the examination of transudates and exudates. The part of the treatise which deals with blood counting is highly valuable, for the detailed care with which this technique is described, ought to result in more accurate blood counts, something which every physician has had frequent occasion to desire. Nothing of any importance has been omitted. Several pages are devoted to the prices generally charged for the various laboratory examinations. It is a book not only for the technician but the physician as well.

THE NEXT HALF CENTURY IN MEDICINE (A SYMPOSIUM). Sterling-Winthrop Research Institute, Rensselaer, N. Y. (No charge).

This 75 page book contains ten addresses made on the occasion of the dedication of the new Research Institute of Sterling-Winthrop. Many of these addresses possess material of urgent importance to everyone interested in medicine. The future of cancer research by C. P. Rhoads is particularly attractive inasmuch as he draws a seemingly justified analogy between the invasive, malignant cell and the pathological, virulent micro-organism or bacterium and infers that, since chemotherapy has been successful in combating infection, so we may hope that substances may be found which will oppress and destroy cancer without injury to normal cells.

William Dock, M. D., points out several ways in which medical practice must be improved in the future, the chief being greater emphasis on team work and the formation of clinic groups of various sizes. While valuing the functions of the

general practitioner, Dock obviously does not envision him as the mainstay of future society.

Professor Albert Szent-Györgyi feels that the immediate future in biochemistry will be concerned with nucleoproteins, attacked on the molecular level,—application of quantum mechanics and the theory of the solid state to protein molecules. Water has not in the past been sufficiently recognized as the center of the whole energy cycle, and in the next 50 years, "the discovery of water" will constitute one of the greatest achievements. Much work is needed on photosynthesis. Team work is essential and pure science, as opposed to applied science, is the desirable motivation.

Other scientific addresses by Loewi, Dubos, Stanley and Klumpp are included.

URGENT DIAGNOSIS, WITHOUT LABORATORY AID. Prof. Dr. Hanns L. Baur, 90 pages, Charles C. Thomas, Springfield, 1950, \$2.00.

Hanns L. Baur, a disciple of Prof. Friedrich von Müller has written a book which is helpful in making a diagnosis without x-ray and laboratory assistance. The necessity of making diagnoses under these conditions usually is met in the presence of urgent and serious conditions, such as unconsciousness, convulsions, sudden psychoses, anuria, vomiting and abdominal pain, all of which Baur carefully describes. While it is true that the majority of the emergencies usually permit the physician sufficient time to verify his diagnosis in the laboratory, it is equally true that our dependence on laboratory assistance has produced a gradual atrophy of those acute powers of observation and of reasoning which characterized many of our distinguished progenitors. To be able to form a quick, unaided opinion of a case merely from the history and physical examination surely represents the first part of every diagnosis, and Baur's book is chiefly valuable in emphasizing for the medical reader the salient points evoked by the various acute manifestations of disease.

GENERAL ABSTRACTS OF CURRENT LITERATURE

SAPHIR, W. AND SPURLOCK, J.: *Alcoholic neuropathy and Lacunae's cirrhosis*. Illinois M. J., 97, 5, 278-280.

A 61 year old Hungarian, accustomed to drinking one quart of wine daily was admitted to hospital, where the double diagnosis of hepatic cirrhosis and peripheral neuropathy was easily made. The role of alcohol in the causation of both conditions is well established, though the exact mode of action is in dispute. In this particular case intravenous thiamine produced very satisfactory resolution of the peripheral neuritis but treatment did not improve the hepatosplenomegaly. It is unusual to find an extensive neuropathy thus associated with alcoholic cirrhosis, and the problem is, why? In this particular case there was a very severe nutritional anemia present on admission and the authors surmise that the resulting anoxia may have rendered the nervous tissues vulnerable. The anemia, incidentally, also rapidly improved.

HILL, A. H.: *A new concept of the cause of Hirschsprung's disease or congenital megacolon, with a new method of treatment by surgery*. Northwest Med., 49, 5, 341-344. Congenital megacolon has been shown to be due to low-grade obstruction from an area of narrowed bowel in the upper rectum and lower sigmoid, which lacks effective peristalsis, and therefore impedes the fecal stream. Pathological examination shows an intrinsic defect in the myenteric nerve supply to this portion of gut. A combined abdominoperineal excision of the area of narrowed bowel, with preservation of the anal sphincter, has been worked out. In five children the operation has produced good results with satisfactory bowel control in every case.

CHRISTIE, A. C., COE, F. O., HAMPTON, A. O. AND WYATT, G. M.: *The value of tannic acid enema and post-evacuation roentgenograms in examination of the colon*. Am. J. Roentgen. and Rad. Therapy, 63, 5, 657-664.

The use of tannic acid (1 gram by weight to 100 c.c. of barium-water suspension) has proved a valuable addition to

the previous methods of examining the colon. The advantages of tannic acid are three-fold: the mixture is sufficiently irritating to stimulate contraction of the entire colon; the tannic acid is astringent and inhibits mucus secretion; the viscosity of the tannic acid causes the barium to adhere to the wall of the bowel.

ROUTLEY, E. F., MANN, C., BOLLMAN, J. L., GRINDLAY, J. H. AND FLOCK, E. V.: *Effects of vagotomy on pancreatic secretion*. Proc. Staff Meet. Mayo Clin., 25, 9, 218-222.

Complete, chronic pancreatic fistulas were established in 30 dogs, and in 9 of these complete supradiaphragmatic vagotomy was performed. It was found that vagotomy has no significant side-effects on the pancreas. It produced no significant impairment of external pancreatic function in the dog. Hence it is unlikely that the diarrhea commonly occurring in patients following vagotomy is to be attributed to disturbance in pancreatic function.

STEVENSON, C. A., MORETON, R. D. AND COOPER, E. M.: *The nature of fictitious polyps in the colon*. Am. J. Roent. Rad. Ther. 63, 89, Jan. 1950.

Fictitious polyps as noted on double contrast roentgenograms of the colon are largely due to air bubbles formed by the introduction of air through fluid barium during the double contrast examination. Unhydrolyzed castor oil, vegetable oil and fats and greases which are liquid at body temperature may cause fictitious polyp formation. The authors' findings are very important for all those who use this very questionable procedure in the roentgenological examination of the colon.

Franz J. Lust.

VOGT, ALFRED: *Oesophagitis*. Fortschr. Roentgenstr. 72, 6, 686, April, 1950.

Three cases of esophagitis are reported. The first one was found in a case of lymphosarcomatosis. In the second there was a lymphogenous leukemia and the third was combined with a peptic ulcer of the esophagus. An accurate method and

technique of examination is essential to attain convincing roentgenograms.

Franz J. Lust.

BOEM, F.: *Roentgenological appearance of healed, formerly ulcerative intestinal tuberculosis*. Fortsch. Roentgenst. 72, 6, 675, April, 1950.

Healing of intestinal tuberculosis leads to characteristic roentgen signs, the explanation of which is based on anatomical findings. These are: fine superficial star-shaped deformations of the mucosal pattern, large patches with atypical slightly polypoid intramural surface, thickening and stiffness of the bowel wall, longitudinal shrinking especially of the colon and intestinal obstruction. Accordingly the normal mucosal pattern shows roughening and deformation, colon seems shortened, colic surface, localized rigidity. The colon seems shortened, the passage is slow. A pouch-like cecum seems characteristic.

Franz J. Lust.

DYSON, F. L.: *Liver damage in ulcerative colitis*. Brit. Med. J., June 3, 1950, 1301-2.

3 cases among 20 of chronic ulcerative colitis presented hepatic and/or splenic enlargement. Autopsy in one case revealed portal cirrhosis. Two of the cases showed anemia, which in one case was profound, although the author does not classify the anemia. Presumably liver damage may occur in ulcerative colitis as a result of poor nutrition and may depend on faulty absorption of such lipotropic factors as methionine and cystine.

BARSLEY, A.: *Sigmoiditis*. Am. J. Proctology, 1, 2, 81-85.

The diagnosis of sigmoiditis rests on sigmoidoscopy and x-ray studies by barium enema. In treatment, hemicellulose, mineral oil and normal saline enemas are permitted. The overnight instillation of iodoform in a mixture of cotton seed oil and cod liver oil as a retention enema is a special form of treatment which should be continued for several weeks.

MARSHAK, R. H.: *Multiple carcinomas of the large bowel*. Radiology, 54, 5, 729-731.

In doing a barium enema examination, one should remember that multiple lesions of the colon are not uncommon. The author presents a case, with illustrations, in which 5 separate cancers of the large bowel were demonstrated radiologically and subsequently proved at operation.

BARGEN, J. A. AND ASSOCIATES: *Symposium on some complications of chronic ulcerative colitis*. (Proc. Staff Meet. Mayo Clin., 25, 10, 239-263).

The local colonic complications of chronic ulcerative colitis occurred in 35 percent of 2,000 cases examined. Polyps developed in 19 percent, strictures in 11 percent, malignant neoplasms in 5 percent, perforation in 2 percent, perforation with fistula formation in 2 percent and massive hemorrhage in only 1 percent. Subclinical glomerulitis is frequently associated with the disease but ulcerative colitis is not an important factor in causing clinical glomerulonephritis. Fatty change of the liver was found at autopsy in 47 of 91 cases and is probably related to the malnutrition, toxemia and debilitating effects of the disease. Cirrhosis was found in only 3 percent, an incidence no higher than that observed in routine necropsies. In 86 consecutive autopsies there were 46 instances of interstitial pancreatitis, as compared with 3 instances in a control group of 86 cases. It does not proceed to the development of chronic, recurring pancreatitis, but it may contribute to the clinical irreversibility of some cases of chronic ulcerative colitis.

SZARZ, T. S.: *Psychiatric aspects of vagotomy*. II.—*A psychiatric study of vagotomized ulcer patients, with comments on prognosis*. Psychosomatic Med., 1949, XI, 4, 187-199.

25 vagotomized ulcer patients were studied from the psychiatric standpoint. It was found that post-operative symptoms usually can be understood in terms of the previous (pre-operative) personality structure. Briefly, it was found that the more psychic energy that is bound by the organic illness (i.e., ulcer symptoms) and by the therapy (diet, etc.)—the more likely are the results of vagotomy to be unfavorable. Con-

versely, the less psychic energy is bound in this manner (i.e., instinctual gratification being derived from being ill and from the medical regime)—the better is the prognosis following vagotomy.

GARLICK, H. W.: *Continuous intragastric drip in the treatment of peptic ulcer*. Med. J. Australia, 1949, 36, 13, 453-455.

The author highly recommends Winklestein's intragastric drip and describes a mixture of milk, skim milk powder, sugar, eggs and vitamins which will provide the patient up to 4000 calories per day in a total volume of 4½ pints. He emphasizes the fact that in cases where the pain of a deep penetrating ulcer cannot otherwise be controlled, it is promptly relieved by the drip method. Furthermore, in many cases of pyloric block the patient can be rehabilitated and prepared for surgery quite easily by 3 weeks of drip treatment, often without intravenous feeding or medication.

MAJUMDER, N. G.: *Analysis of the sufferings in the tea gardens in Dooars*. J. Indian Med. Assn., Oct. 1949, 19, 1, 16-17.

Morbidity and mortality are high among the aboriginal class who work in the tea gardens in Dooars, because of a poor climate,—heavy rainfall, dense forests and dampness. While malaria is the commonest disease, dysentery, undiagnosed diarrheas, pneumonia, tuberculosis, anemia and nephritis are very common. Bowel disease forms 16 per cent of the cases of illness and is due to impure drinking water. Hookworm is universal but does not produce much disability. Obviously the situation calls for mass hygienic and food measures.

GARROD, L. P. AND McILHAY, M. B.: *Hospital outbreak of enteritis due to duck eggs*. Brit. Med. J. Dec. 3, 1949, 1259-1261.

A description of an outbreak of *Salmonella typhi-murium* enteritis involving nurses, female staff and patients in a large general hospital. This was found to be due to eating a lightly cooked pudding containing 200 duck eggs which had been procured from 16 farms, at 2 of which conditions were discovered to be unsanitary. One elderly woman died from the infection. Sixty persons were contaminated. It has been recognized for 20 years that duck eggs, unlike hens' eggs, may contain pathogenic bacteria of the *Salmonella* group, owing to infection of the bird itself.

MACFARLANE, J. A. AND KAY, S. K.: *Ogilvie's syndrome of false colonic obstruction: is it a new entity?* Brit. Med. J. Dec. 3, 1949, 1267-1269.

The authors describe 3 cases in which, pre-operatively, the diagnosis of organic obstruction of the colon was made, but at which operation revealed in 2 cases no obstruction whatever and in the third case merely a ring of firm contraction in the pelvic colon, which disappeared during further anesthesia. It is safe to state that these were examples of spastic ileus. It is argued that in the cases described by Ogilvie, by Dunlap and by Handley, spastic ileus may have been the appropriate diagnosis, even though in their cases malignant infiltration was found retroperitoneally in the subdiaphragmatic area, giving rise to the belief that an imbalance of sympathetic-parasympathetic innervation had occurred owing to involvement of the celiac plexus. As matters stand, it appears that spastic ileus may result from such celiac plexus lesions, or that it may result from causes which are at present unrecognizable.

QUATTLEBAUM, F. W.: *Acute pancreatitis*. Journal-Lancet, Dec. 1949, 69, 12, 418-425.

That form of an acute pancreatitis which consists in acute edema of the pancreas is the more common, while the acute hemorrhagic pancreatitis is less common. The serum amylase test is the greatest single aid in diagnosis. Treatment should be conservative whenever possible. Constant intragastric suction and parenteral feeding are of primary importance in order to avoid the pancreatic stimulation which oral feeding always produces.

ROSE, T. F.: *Perforated peptic ulcer: the mortality and morbidity of treatment*. (Med. J. Australia, April 1, 1950, 421-425).

Rose regards the non-operative treatment of perforated

AMER. JOUR. DIG. DIS.

peptic ulcer as risky, because a suction tube will not prevent leakage from a perforated ulcer whose edges are calloused. It is possible that some of the excellent results reported in treatment by tube and antibiotics alone depended on a certain percentage of incorrect diagnoses. Rose passes a tube into the stomach to keep it as empty as possible as soon as the diagnosis is made and leaves it there into the post-operative period. The administration of penicillin is a routine measure. In his best series, 28 patients were operated upon with 4 deaths. He does not mention the amount of penicillin employed, but it may possibly have been less than the massive doses used in several American and British series with almost no mortality.

PORTES, C.: *Malignant rectal polyps: fulguration versus resection as treatment of choice.* (Am. J. Proctology, 1, 1, 17-25).

Portes describes 25 cases of malignant rectal polyps treated, thus far successfully, by fulguration. Early, single, non-invasive carcinomatous polyps of the rectum and rectosigmoid can be treated safely and favorably by fulguration. There seems justification in continuing this method of treatment so long as patients are kept under frequent observation.

WILSON, T. E.: *Rectal prolapse.* (Med. J. Australia, April 8, 1950, 461-465).

In prolapse in children, the best method of treatment is giving subcutaneous injections of 5 percent phenol in oil. Partial prolapse in adults is best treated by a ligature operation. For complete prolapse, recto-sigmoidectomy is advised. If this operation already has been performed, then it may either be repeated or Moschowitz's operation, Roscoe Graham's procedure or the insertion of silk slings across the pelvis may be employed. Where the patient's condition is very poor, or mental cooperation lacking, Thiersch's operation is preferred.

KNEIDEL, J. H.: *The use of a preliminary roentgenogram of the abdomen in the diagnosis of congenital obstruction in the intestine.* (Am. J. Roentgen & Rad. Ther., 64, 3, 430-441).

In various forms of congenital obstruction in the bowel, the preliminary film of the abdomen contributed information essential to the final diagnosis. Important features seen on the preliminary film include: gas-distended loops of intestine of widened caliber; when this dilated intestine shows no abrupt termination and has a mottled appearance, meconium ileus must be considered. A large, dilated stomach, associated with reduced amounts of gas in the intestine suggests high obstruction.

OFFENKRANTZ, W. G.: *Water-soluble chlorophyll in the treatment of peptic ulcers of long duration.* (Rev. Gastroent., 17, 5, 359-367).

A total of 79 patients with x-ray proved duodenal and gastric ulcers were treated with Chloresium Powder (Rystan), containing water-soluble chlorophyll, a coating material and recognized antacids. Of the 74 patients having no pyloric obstruction, 58 showed, on roentgen examination, complete healing in from 2 to 7 weeks. Most patients experienced symptomatic relief in from one to three days. Patients were permitted to use tobacco, alcohol and normal diets. The effects of chloronium should be further investigated as chlorophyll gives promise of usefulness in peptic ulcer.

MORRISSEY, D. M.: *Gastric ulcer occurring after vagotomy.* (Brit. M. J., Sept. 16, 1950, 651-653).

In a series of 79 cases of duodenal ulcer, two cases developed gastric ulcer following successful vagal section, within 6 months of the operation. Vagotomy does not seem suitable as a treatment of gastric ulceration. In the cases described, there was every reason to believe that the vagal section had been complete.

FRIEDMAN, R. L. AND EPSTEIN, B. S.: *Benign gastric ulcer of the greater curvature.* (Radiology, 55, 3, Sept. 1950, 398-402).

The authors describe 2 histologically verified cases of benign ulcer of the greater curvature. One patient survived 14 months after the operation and is now in good health. The other died of a concomitant pulmonary tumor. It is suggested that the

presence of an ulcer crater on the greater curvature toward which the rugal folds converge may be benign, but operative intervention is nevertheless urged.

PALMER, W. L., KIRSNER, J. B. AND LEVIN, I.: *The treatment of intractable peptic ulcer.* (Ann. Int. Med., 33, 3, Sept. 1950, 590-601).

Intractability sometimes applies to the ulcer, more frequently to the patient personally. When gastric ulcers do not heal, cancer should be suspected and gastric resection carried out. Intractability in duodenal ulcers usually is due to inability to control acid secretion. Radiation therapy of the stomach is helpful here. In jejunal ulcer, vagotomy is the treatment of choice. Occasionally only must a total gastrectomy be done for ulcer recurring after partial gastrectomy.

LAHEY, F.: *Ulcerative colitis.* (Rev. Gastroent., 17, 9, 723-736).

In cases of ulcerative colitis which do not do well on medical management, Lahey does an ileostomy which permits the patient to live in complete comfort. The colon should be resected before joint changes occur. The ileostomy should be done before the case becomes desperately toxic. Colectomy should be done to prevent bleeding. There is growing evidence that the patient who retains his colon is a candidate for an increasing percentage of carcinomas.

SILVERSTEIN, S.: *Subhepatic cecum and appendix.* (Miss. Valley M. J., 72, 5, 145-149).

A case of subhepatic cecum and appendix is described. A congenital, inverted cecum can be made to return to its right iliac fossa in some cases, by a change in posture from the recumbent to the upright position, provided there are no adhesions. The diagnosis of subhepatic cecum and appendix is best established by contrast ingestion, barium enema and a good clinical history.

FINDLEY, J. W.: *The clinical significance of chronic gastritis.* (American Practitioner and Dig. Treat., 1, 9, 920-922).

Findley feels that although chronic gastritis is a frequently found gastroscopic and histologic entity, it is of little clinical significance and scarcely needs treatment. In some instances it is associated with bleeding from the stomach. It has not been shown to predispose to the development of cancer. Giant hypertrophic gastritis is important in that it may be mistaken for tumor.

GILLMAN, J. AND GILLMAN, T.: *Structure of the liver in fatal burns.* (S. African J. Med. Sci., (1948) 13, 169-181).

An examination of the livers of 38 cases dying from burns, within one hour up to 36 days after the accident, disclosed 3 main types of reactions, viz., loss of stainability of liver cells, fatty changes, and atrophy of cells in the central zone of the lobule. Loss of stainability was seen mainly in livers of cases dying within 9 hours and between 36 and 48 hours, and this reaction was confined mainly to the region around the central vein. Fat, in the form of small and medium sized droplets, could appear as early as 18 hours but was more constantly observed between 36 and 72 hours after the accident. From an analysis of the time sequence of the fatty changes, it was suggested that the development of a very fatty liver requires at least 8 days. Atrophy of cells around the central vein first becomes manifest at 36 hours after burns. Mild necrosis was suggested in only one case. The extensive necrosis reported from different parts of the world was not found in the present series. Tannic acid intensifies the tendency to necrosis. The morphological changes found in the liver were insufficient to account for death. If the liver does contribute to death it does so at the chemical level and not the histological level.

MODLIN, H. C.: *Ulcer, phobia and narcolepsy.* (Bull. Menninger Clinic, Vol. 12, No. 6, 203-209).

The author presents a case of recurring peptic ulcer in great detail from the psychological standpoint. The case is of interest because, while it conforms exactly to the classical ulcer picture in some respects, it deviates in others, particularly in the development of anxiety neurosis and narcolepsy supplementary to the ulcer syndrome. (Narcolepsy representing the retreat of a passive-dependent personality into hypersomnolence is not usually found in persons with peptic ulcer).

THENFADIL HCL TABLETS AVAILABLE NATIONALLY

Thenfadil hydrochloride, antihistamine drug for the relief of systemic allergies, previously available in limited quantity, is now being distributed nationally by Winthrop-Stearns Inc. in 15 mg. tablets. The tablets come in one packing, bottles of 100's, and are sold on prescription.

Company literature, prepared for physicians, notes a high efficiency and good tolerance for Thenfadil in the control of asthma, hay fever, rhinitis and other allergies. Reports of clinical investigations disclose a low incidence of side effects. Most observers, the literature states, have found the effective adult dose ranges from 15 to 90 mg, 1 to 6 tablets, daily in divided doses.

The chemical name is N, N-dimethyl-N'-(3-thenyl)-N'-(2-pyridyl) ethylenediamine hydrochloride. Thenfadil is also available in combination with the decongestant Neo-Synephrine as a nasal spray for treatment of allergies.

ACETOXY-PRENOLON

Manufacturer: Schering Corporation, Bloomfield, New Jersey.

Active Constituent: 21-acetoxypregnenolone (delta-5-pregnene-3-beta, 21-diol-20-one-21-acetate) in sterile aqueous suspension.

Indications: Clinical trial in patients suffering from rheumatoid arthritis has resulted in subjective and objective improvement in many instances.

Toxicity: No side actions of any importance have been reported. Local irritation, if any, should be treated by appropriate local measures.

Dosage: Although a definite dosage schedule has not yet been established, the useful range is from 50 to 300 mg. daily. Suggested dosage schedule found to be effective is: 100 mg. the first day, 200 mg. the second day, and 300 mg. daily thereafter for a total of 14 days; then 200 mg. every second day for 30 to 60 days of therapy. Further treatment should be based on response attained.

Packaging: Multiple dose vials of 10 cc., containing 100 mg. per cc. containing 100 mg. per cc. in aqueous suspension.

SCHERING FIELD STAFF INCREASED

The addition of eighteen new representatives to Schering's Professional Service Staff has recently been announced by Mr. Francis C. Brown, president of Schering Corporation of Bloomfield and Union, New Jersey, manufacturers of endocrine and pharmaceutical preparations for the medical profession.

Fifteen of the new Representatives have been assigned to the Domestic Sales Division for service in various territories throughout the country. Prior to assuming their duties they completed an intensive four weeks training course in scientific and technical fields and in professional service. Three new Representatives of Schering's International Division also completed the training course and are now serving in Puerto Rico and Canada. The selection and training of these men maintains the Schering policy of providing well-trained and qualified Representatives in the field to better serve the medical and pharmaceutical professions.

DR. SEBRELL

Dr. William H. Sebrell was recently appointed director of the National Institutes of Health, Public Health Service. The appointment was made by Dr. Leonard A. Scheele, Surgeon General of the Public Health Service. Dr. Sebrell will succeed Dr. Rolla E. Dyer, whose retirement from the Federal Service October 1, was recently disclosed.

Dr. Scheele, in reviewing Dr. Sebrell's career said: "Dr. Sebrell, in addition to being a leading authority on nutrition has had long and varied experience in other fields of medical research."

He began his research career under Dr. Joseph Goldberger, the world-famous Public Health Service scientist who discovered that pellagra is a dietary-deficiency disease," Dr. Scheele continued. "After Dr. Goldberger's death, in 1929 Dr. Sebrell continued to work on pellagra, and then branched out into the general field of the vitamin B complex, and has made many important contributions to our knowledge of dietary needs and deficiencies. An outstanding accomplishment was the first recognition of the dietary deficiency disease

ariboflavinosis. Dr. Sebrell has also done major work on the role of diet in cirrhosis of the liver, and on the anemias," the Surgeon General said.

Dr. Sebrell was appointed director of the Experimental Biology and Medicine Institute, which was formed in 1948 by a consolidation of several existing laboratories at the Public Health Service's National Institutes of Health. Before that he was head of the Laboratory of Physiology. During World War II he acted as co-director, with M. A. Wilson of the United States Department of Agriculture, on the National Nutrition Program, which coordinated the activities of all state agencies working in the field of nutrition. The work accomplished under this program materially aided in the production of food and the maintenance of civilian health during the war years. Temporarily assigned to the U. S. Army in 1945, he helped inaugurate a system for determining the nutritional status of civilians in occupied Germany. He served as an expert on the survey team which restudied the State of German nutrition in 1948. That survey contributed to changes in the German diet designed to make Germans more self sufficient.

Dr. Sebrell aided in drawing up the first international standards of nutrition for the League of Nations, and has made many nutritional surveys for various governments and international organizations, such as the Pan-American Sanitary Bureau. In addition to this international work and his own laboratory research, he has pioneered in gaining acceptance of scientific nutrition as a regular function of modern state and local health departments in this country.

In recognition of his research achievements, Dr. Sebrell has received the Mead Johnson Award of the American Institute of Nutrition, and the Research Medal of the Southern Medical Association. For his work in Germany, he received the Army Legion of Merit. He is a member of the National Research Council and of the visiting lecturer staff of George Washington University Medical School.

Born in Portsmouth, Virginia, in 1901, Dr. Sebrell received his medical degree from the University of Virginia. Immediately after graduation he entered the Commissioned Corps of the Public Health Service.

ice as an Assistant Surgeon. He now holds the rank of Medical Director.

DR. J. C. CUTLER

Dr. John C. Cutler has returned to this country after two years of duty in India. Dr. Cutler will enter the School of Public Health, Johns Hopkins University. He has been on loan as Consultant to the Indian Government and head of a World Health Organization venereal disease team which demonstrated latest penicillin techniques in the treatment of syphilis. In addition to establishing a laboratory and clinic at Simla, India, Dr. Cutler made a survey of venereal disease in Afghanistan and in the Bombay area of India.

Prior to his service with the Indian Government, Dr. Cutler did research in Guatemala for two years in the epidemiology of syphilis and false positive serology. He was cited by the Republic of Guatemala "for his important services to the National Army of the Revolution, with regard to the personal health of the armed forces and his meritorious cooperation with the Army Medical Department."

A native of Cleveland, Ohio, Dr. Cutler received his B. A. and M. D. degrees from Western Reserve University in 1937 and 1941. After interning at the U. S. Marine Hospital, Staten Island, N. Y., he was commissioned in the Regular Corps, USPHS on July 20, 1942 and now holds the rank of Senior Surgeon. Following his commission, he saw service with the U. S. Coast Guard, with the USPHS Narcotics Hospital, Lexington, Ky., and with the Venereal Disease Research Laboratory, Staten Island. He then guided experimental studies in gonorrhea involving use of volunteers at the Federal Penitentiary in Terre Haute, Indiana. He did further research at Staten Island on evaluation of penicillin therapy in early syphilis before his assignments to foreign duty.

A. C. T. H.

Clues to the role in psychosis of ACTH, cortisone and similar hormones will be studied in a cooperative project by the National Institute of Mental Health of the Public Health Service, and the Worcester

Foundation for Experimental Biology, Shrewsbury, Massachusetts.

Recent evidence points to a relation between these hormones and mental illness. The new investigations at the Worcester Foundation will be renal cortical hormones in schizophrenic patients and in well persons. New techniques of hormone analysis used by the Foundation promise to reveal facts about specific chemical mechanisms that may help explain certain types of mental illness. From such basic studies, it is hoped, new methods of treatment may eventually be developed.

The joint project will be under the direction of Dr. Hudson Hoagland, Executive Director of the Worcester Foundation and consultant to the Public Health Service's National Institute of Mental Health.

Also cooperating in the project will be the Worcester State Hospital, which has worked with the Foundation in preliminary studies. Research activities at the Hospital will be directed by Dr. Nathan Kline. When the new clinical center at the National Institutes of Health, Bethesda, Maryland, is completed, work along these lines will also be carried out by the National Institute of Mental Health staff at the center.

V. D.

Other countries should consider the United States the place of choice for training health personnel for combating venereal disease throughout the world according to a report by a World Health Organization (WHO) expert committee.

The report, prepared by the WHO Syphilis Study Commission which visited the United States in the summer and fall of 1949, declares that the method of venereal disease control developed in the United States can be usefully applied in many areas of the world.

"The USA is, at present, the place of choice for the study of venereal disease problems and control methods, and this should be borne in mind in directing the training of personnel for combating venereal disease throughout the world," the report asserts.

Surgeon General Leonard A. Scheele of the Public Health Service, said in announcing distribution

of the report that it is one of the most complete and expert studies ever made of U. S. venereal disease control methods. "The evaluation of penicillin therapy in syphilis as well as other phases of the report should prove of great value to specialists in venereal disease," he said.

More than 1,000 copies of the report are being distributed to medical schools, medical journals, state and city health officers, venereal disease control officers, rapid treatment centers, and other interested organizations and individuals.

"The value of penicillin in the treatment of syphilis was an outstanding U. S. discovery," the report states. "This antibiotic is capable of rendering non-infectious, in a rapid and safe manner, nearly all cases of open lesions within a short period of time. The application of this non-toxic antibiotic, especially when contained in absorption-delaying vehicles, will make possible the mass treatment of syphilis, other treponematoses, and gonorrhea in different areas of the world with a high prevalence of disease."

"The venereal-disease control methods used in the USA are a useful guide in planning future programmes elsewhere," the report states. "The U. S. venereal disease control programme, consisting of decentralized units voluntarily connected with a central advisory body, has achieved results which other nations, working on their own initiative and co-operating on an international basis, might emulate with broadly similar programmes."

TYLOSTERONE

"Eli Lilly and Company announces the release of TABLETS 'TYLOSTERONE' (Diethylstilbestrol and Methyltestosterone, Lilly). Heretofore, estrogens and androgens have been employed simultaneously on a basis that was largely tentative. It was theorized that when used together, they would avoid uterine bleeding and virilization while giving relief from menopausal symptoms. Now, there is conclusive clinical evidence, obtained in such a way as to preclude both prejudice and psychotherapeutic suggestion, that the combination contained in 'Tylosterone' does minimize the undesirable side-effects of estrogen alone, and furthermore, it affords

HABIT TIME OF BOWEL MOVEMENT



SAFE . . .

PETROGALAR[®], given at bedtime—not with meals—has no adverse effect on absorption of nutritive elements. It provides a relatively small but highly effective dose of mineral oil augmented by a bland, hydrophilic colloid base. The result is a soft-formed, easily passed stool, permitting comfortable bowel movement.

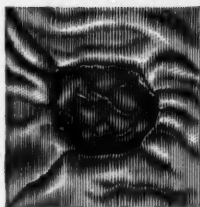
If preferred, PETROGALAR may be given thinned with water, milk, or fruit juices—with which it mixes readily.



Wyeth Incorporated, Phila. 2, Pa.

in peptic ulcer

controls symptoms



...speeds healing

RESINAT protects the ulcer crater by inactivating gastric pepsin and adsorbing excess acidity, without producing acid rebound or systemic alkalinization.

RESINAT is insoluble, chemically and physiologically inert. It does not remove chlorides, phosphates, vitamins or minerals from the body.

RESINAT, the original medical application of anion exchange resins in the treatment of peptic ulcer, is now available in plain tablet form. Correct dosage. Quicker disintegration. Faster action.

How Supplied: Plain Tablets each 0.5 Gm. In bottles of 36, 100, and 1000.

Also available in Capsules (0.25 Gm.), Sugar-coated Tablets (0.5 Gm.), Powder (1 Gm.).

RESINAT

brand of polyamine-methylene
resin for peptic ulcer



Literature and samples on request



The National Drug Company
Philadelphia 44, Pa.

more than half a century of service to the medical profession

A
Cholecystopaque
with
minimum



SIDE EFFECTS

Monophen

Modern **MONOPHEN** reduces to an absolute minimum the cramps, diarrhea, dysuria, and other side reactions heretofore associated with present cholecystographic procedure. In addition, **MONOPHEN** provides a diagnostic trustworthiness attested to by its use in over 3000 cases* . . . with complete confirmation of those cases where surgical intervention was recommended.

Normal **MONOPHEN** cholecystograms are uniformly excellent, reveal homogeneous opacity and adequate contraction after the fat meal.

• **MONOPHEN** is 2-(4-hydroxy-3, 5-diiodo-benzyl)-cyclohexane carboxylic acid, containing 52.2% iodine in stable combination.

• **SUPPLIED IN BULK:** Capsules (0.5 gram each) are cellophane-sealed in units of 2's and boxed in quantities of 50, 100, 250, 500 and 1000, with a requisite number of dispensing envelopes imprinted with directions for use.

Write for samples

*Preliminary
report
available.



NATIONAL SYNTHETICS, INC.
270 LAFAYETTE STREET, NEW YORK 12, N. Y.

"Dependability Through the Years"

Introducing

without oil



TURICUM

TRADE MARK

HYDROPHILIC LUBRICOID

Whittier
LABORATORIES

DIVISION NUTRITION RESEARCH LABORATORIES, INC. • CHICAGO 11, ILLINOIS

ADVERTISERS' INDEX

Abbott Laboratories VI
 American Meat Institute III

Bio-Ramo Drug Co., Inc. II

The S. E. Massengill Co. VII

The National Drug Co. XI

National Synthetics, Inc. XII

Parke, Davis & Co. VIII

Chas Pfizer & Co. Inc. 3rd Cover

G. D. Searle & Co. 4th Cover

Whittier Laboratories IV & V

Whittier Laboratories XIII

Winthrop-Stearns, Inc. I

Wyeth Incorporated 2nd Cover

Wyeth Incorporated X

an increased feeling of well-being while relieving the symptoms of menopause. In proper dosage, 'Tylosterone' provides objective and

subjective relief, without side-effects. Formula: Diethylstilbestrol—0.25 mg. Methyltestosterone—5 mg."

BETA GLUCURONIDASE

The Sigma Chemical Company (St. Louis, Mo.) is now the first commercial producer of Bacterial Beta-Glucuronidase.

This enzyme is rapidly being recognized for the vital role it plays in biochemical processes. New research programs are starting around the world to study the occurrence and function of Beta-Glucuronidase in all tissue and body fluids.

Beta-Glucuronidase, Bacterial, SIGMA, will quantitatively hydrolyze Phenolphthalein Glucuronide in a very short time and at pH 7.0, whereas the optimum pH for mammalian Glucuronidase is 4.5.

Beta-Glucuronidase, Bacterial, SIGMA, is available as a prepared solution (pH 7.0), or as a dry powder which can be reconstituted with distilled water to yield a buffered solution directly. Stability is good.

NEW STEROID OFFERS TISSUE-BUILDING WITH MINIMAL SEXUAL STIMULATION

Organon, Inc., of Orange, N. J., has just introduced to physicians Stenediol, known under the generic name of mestenediol (methyl androstenediol), thus making commercially available for the first time a steroid which possesses the anabolic actions of testosterone without to the same extent causing virilization. Stenediol will find great usefulness in many conditions, especially in women and children in whom it may be desired to build tissue without evoking the strong stimulation of secondary sex characteristics usually produced by testosterone.

Stenediol 'Organon' is available in aqueous suspension for intramuscular injection and in scored buccal and oral tablets. Each cc of Stenediol injectable contains 25 mg of mestenediol as fine crystals suspended in an aqueous vehicle made isotonic with dextrose and containing 0.45% phenol as a preservative. The oral and buccal tablets each contain 10 or 25 mg of mestenediol.

Stenediol (mestenediol) 'Organon' is a near-relative of testosterone and possesses anabolic action causing the retention of nitrogen and the deposition of body protein. It has, however, little or no tendency to cause virilization in the dosages used thus far. This is of especial value in the treatment of retarded growth and certain endocrine deficiencies and constitutional diseases accompanied by protein wastage, negative nitrogen balance, or failure to build body protein.

The average dosage of Stenediol employed has been 25 mg orally, buccally, or intramuscularly two to five times a week. In children, a suggested initial dosage is from 5 to 10 mg one to three times a week. In any event, the dosage must be adjusted so that the adrogenic effect will be held to the minimal desired in the individual case.

Stenediol injectable is available in 10-cc multiple-dose vials, boxes of 1 and 6. The 10-mg buccal and oral tablets are available in bottles of 30 and 100. The 25 mg buccal and oral tablets are available in bottles of 15 and 100. Descriptive literature is available on request.

AMER. JOUR. DIG. DIS.



A Handsome Permanent Binder for the American Journal of Digestive Diseases.

Only \$3.50 each
 2 or more at \$3.00 each

Made of a good grade imitation leather, holds 12 issues, one year. Easy to bind in a few minutes in your own home. Stamped on backbone with year and volume number. When ordering it is advisable to give thickness of each full year's issues.

Order Today

Suckert Loose Leaf Cover Co.
 234 W. Larned St., Detroit 26, Mich.

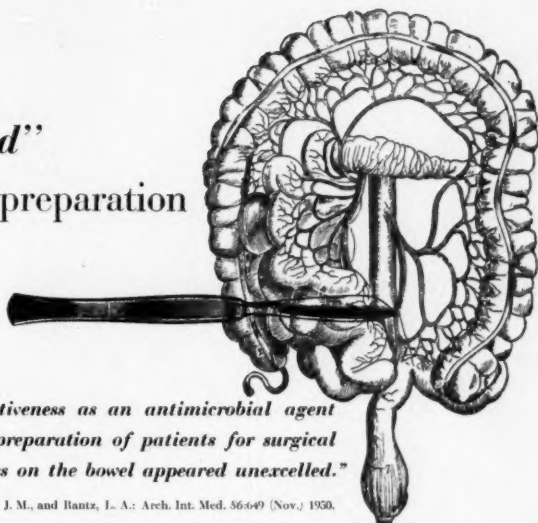
Please send binders of The American Journal of Digestive Diseases for the years

..... Will remit \$.....
 in 10 days or return binders at your expense.

Name

Address State

"unexcelled"
in surgical preparation



*"Its effectiveness as an antimicrobial agent
in the preparation of patients for surgical
measures on the bowel appeared unexcelled."*

Di Caprio, J. M., and Bantz, L. A.: Arch. Int. Med. 56:649 (Nov.) 1930.

CRYSTALLINE
Terramycin
HYDROCHLORIDE



Clinical findings covering a wide range of bacterial and rickettsial as well as several protozoan infections indicate that:

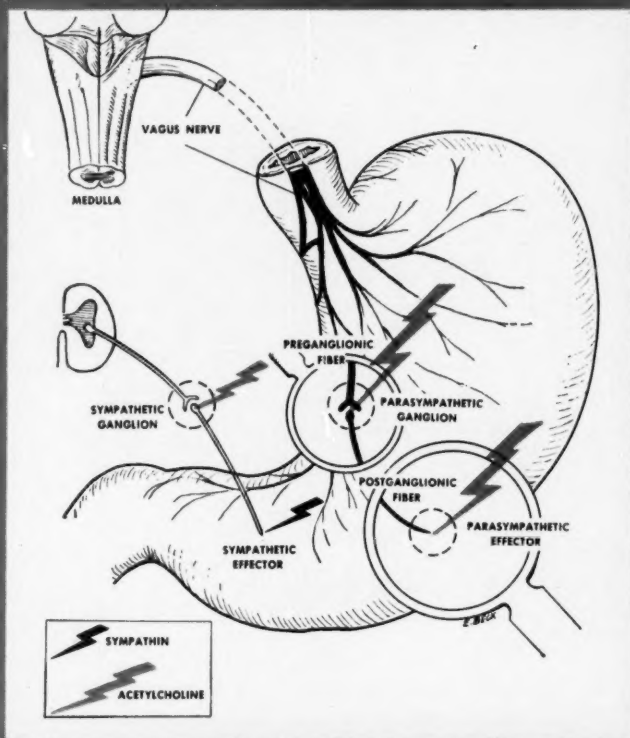
- 1. Terramycin may be highly effective
even when other antibiotics fail.*
- 2. Terramycin may be well tolerated
even when other antibiotics are not.*

Supplied: 250 mg. capsules, bottles of 16 and 100;
100 mg. capsules, bottles of 25 and 100;
50 mg. capsules, bottles of 25 and 100.

Antibiotic Division



CHAS. PFIZER & CO., INC., Brooklyn 6, N.Y.



Banthine^{*} Brand of Methantheline Bromide

BROMIDE

—a true anticholinergic drug, opposes the action of acetylcholine at the ganglions of the parasympathetic and sympathetic systems and at the nerve endings of the parasympathetic system.

Thus, it consistently decreases the hypermotility and in most cases the hy-

peracidity characteristic of ulcer diathesis.

Experience indicates that patients may be best served by prescribing two tablets of Banthine (100 mg.) every six hours day and night although a few patients may be satisfactorily treated with one tablet (50 mg.) on the same schedule.

^{*}Banthine is the trademark of G. D. Searle & Co., Chicago 80, Illinois

RESEARCH IN THE SERVICE OF MEDICINE **SEARLE**